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CELL BIOLOGY

Cell Kinetics

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KINETIC METHODS AND MODELS

1. LASER FLOW CYTOFLUOROMETRIC ANALYSIS OF HTC CELLS SYNCHRONIZED WITH HYDROXYUREA, NOCODAZOLE AND APHIDICOLIN.

Miller-Faures A, Michel N, Aguilera A, Blave A, Miller AO
(c/o Miller) Lab. Molecular Biochemistry, Faculty Medicine, Mons State Univ., 7000 Mons, Belgium
Cell Tissue Kinet; 14(5):501-514 1981

The technique of laser flow cytofluorometry has been used to monitor the arrival in G1 and the subsequent progression through the cell cycle of HTC cells accumulated in metaphase

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with colcemid alone or after treatment with hydroxyurea and Nocodazole. Under the experimental conditions use d in this study, the latter procedure gives much better results, avoiding in particular the extensive formation of micronucleated cells. Aphidicolin, an inhibitor of DNA polymerase, in combination with Nocodazole, provides a useful method to tightly synchronize these cells at the G1/S border. (Author abstract) (20 Refs)

2. RATES OF INCORPORATION OF RADIOACTIVE MOLECULES DURING THE CELL CYCLE.

Gray JW, Pallavicini MG, George YS, Groppi V, Look M, Dean PN
Lawrence Livermore Natl. Lab., Biomedical Sciences Div., Univ. California, Livermore, CA, 94550
J Cell Physiol; 108(2):135-144 1981

The incorporation of tritiated thymidine (3H-TdR) and 35S-methionine were studied, using a cell-sorter-based technique that does not require cell synchronization. Lewis lung tumor (LLT), KHT, Chinese hamster M3-1, and Chinese hamster ovary (CHO) cells were labeled in vitro with 3H-TdR. S-49 mouse lymphoma cells were labeled in vitro with 3H-TdR and 35S-methionine. KHT cells injected into the hind leg of C3H/HeJ mice were labeled in vivo with 3H-TdR. The relationship between the incorporation of 3H-TdR and DNA content was measured. The results indicate that in all five cell populations, 3H-TdR incorporation was lowest early in S-phase, maximal in mid- to late-S-phase, and reduced at the end of S-phase. The degree of variation depended on cell type: in LLT it was two-fold throughout S-phase; in M3-1 cells it was fivefold. In LLT cells treated with cytosine arabinoside, 3H-TdR incorporation decreased five- to eightfold, being low in early S-phase, elevated at about one third of the way through, and high in late S-phase. This is important in considering the interpretation of DNA measurements for cell populations treated with drugs. The S49 results indicate that the cell-sorter technique can be used to measure the uptake of other labeled molecules, or to carry out other types of assays. (23 Refs)

3. GROWTH OF HUMAN MAMMARY EPITHELIAL CELLS ON COLLAGEN GEL SURFACES.

Yang NS, Kube D, Park C, Furmanski P
Dept. Biology, Michigan Cancer Foundation, Detroit, MI, 48201
Cancer Res; 41(10):4093-4100 1981

We have developed a method for sustained growth of human mammary epithelial cells in monolayer cultures. Epithelial organoids derived from solid breast tissues were grown on the surface of thin (approx 1 mm) collagen gel layers in an enriched growth medium supplemented with hormones, growth factors, fetal calf serum, and horse serum. To transfer the cultures, the collagen layers were dislodged and digested with collagenase. The monolayers of cells released into suspension were then dissociated into single cells using trypsin-ethylenediaminetetraacetate. Dissociated single cells were repleted with 75 to 95% efficiency onto collagen layers or tissue culture plastic surfaces. The dissociated cells could also be cryopreserved and reactivated with greater than 80% plating efficiency on collagen layers. Normal human mammary epithelial cells grown under these conditions progressed through 12 to 15 *population doublings*. The population-doubling times for normal and malignant mammary cells on collagen layers were 34 and 65 hr, respectively. After reaching confluence, cells in some cultures, derived from either normal or malignant tissues, penetrated the gel surface and grew into the collagen. Within the gels, the cells became organized into three-dimensional tubular structures. The use of collagen layers eliminates a major problem in growth of human mammary epithelial cells in culture, difficulty in efficient dissociation, and cell transfer from monolayers. (Author abstract) (11 Refs)

4. CLINICAL USEFULNESS OF 67GA UPTAKE RATIO MEASUREMENT IN LUNG CANCER.

Sugawara T, Tanaka O, Iguchi H
Dept. Radiology, Jichi Medical Sch., Minamikawachi-machi, Tochigi Prefecture 329-04, Japan
Nippon Igaku Hoshasen Gakkai Zasshi; 41(6):539-543 1981

Uptake ratios of 67Ga-citrate were measured in 21 primary lung cancers, of which vol-doubling times (DT) were simultaneously determined from sequential films taken at a mo interval or so prior to treatment. This analysis was to determine whether 67Ga-citrate uptake ratio was a useful technique to assess growth rate of tumor. Uptake ratio was expressed as ratio of net cpm of the tumor to that of corresponding region in the opposite lung field, and corrected by the tumor vol and by the attenuation factor related with tumor depth. Study has demonstrated the presence of the significant negative correlation (p less than 0.001) between tumor uptake ratios with 67Ga and DTs, that is, net uptake ratio was increased with a decrease in DT. The different types of lung cancers were ranked with regard to their increasing uptake ratios: adenocarcinoma, squamous cell carcinoma and anaplastic carcinoma, while DTs were decreasing inversely. It was also observed that, in squamous cell carcinoma, increase in tumor vol caused decrease of 67Ga tumor uptake ratio. Measurement of 67Ga-citrate tumor uptake ratio is considered to contribute to estimate the rate of tumor growth. (Author abstract) (17 Refs) (In JPN)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

5. FLOW CYTOMETRY OF BREAST CARCINOMA: II. RELATION OF TUMOR CELL CYCLE DISTRIBUTION TO HISTOLOGY AND ESTROGEN RECEPTOR.

Olszewski W, Darzynkiewicz Z, Rosen PP, Schwartz MK, Melamed MR
(c/o Melamed) Dept. Pathology, Memorial Sloan-Kettering Cancer Center, 1275 York Ave., New York, NY, 10021
Cancer; 48(4):985-988 1981

Flow cytometry analysis of cell cycle distribution was carried out on acridine-orange-stained cell suspensions freshly prepared from carcinoma of the breast of 90 women, and compa red with control, benign breast specimens from 10 women. There was a significantly greater proportion of cells in S (9.1% +-5.8) and G2 + M (8.0 +-6.0) phases of the cycle in breast cancer specimens than in the S (1.5% +-0.6) and G2 + M (2.5 +-0.9) phases of the cycle in benign, control specimens of breast tissue. Great variation was noted among the breast cancers, with medullary carcinomas having the highest percentage of cells in S + G2 + M, and papillary, tubular, colloid and well-differentiated duct carcinomas having the lowest. Tumors from premenopausal women classified as estrogen receptor negative had significantly more cells in S + G2 + M than did tumors from postmenopausal women that were estrogen-receptor positive. (Author abstract) (13 Refs)

6. DURATION OF CELL CYCLE PHASES AND PROLIFERATIVE POOL OF HUMAN CHORIONEPITHELIOMA, BREAST CARCINOMA, LARYNGEAL CARCINOMA, AND LUNG CARCINOMA TRANSPLANTED IN ATHYMIC MICE.

Revazova ES, Petrova AS
All-Union Cancer Res. Center, Moscow, USSR
Vestn Akad Med Nauk SSSR; (7):31-34 1981

Surgery specimens of human chorionepithelioma, and carcinoma of the breast, larynx and lung were transplanted sc into athymic BALB/c mice. When the tumors reached the wt of 1-3 g, animals received ip injection of 3H-thymidine. Animals were sacrificed within different time periods after label administration, and the frequency of labeled tumor cells was determined. Duration of the cell cycle and the proliferative pool of transplanted human tumors were similar to that in transplantable primary murine tumors, but the duration of G2 phase was similar to that in the primary human tumors. (15 Refs) (In RUS)

7. KINETICS OF CELL PROLIFERATION IN SPONTANEOUS MAMMARY TUMOUR IN MICE OF LINE C57BL.

Botev BA, Topashka-Ancheva MN, Karaivanova MH
Oncology Res. Inst., Sofia Medical Acad., Sofia, Bulgaria
Dokl Bolg Akad Nauk; 34(4):561-564 1981

The results of an autoradiographic study of a spontaneous, transplantable C57BL mouse mammary tumor are reported. The tumor cell population was characterized by a short cell cycle and a relatively low cell loss, which permitted the progressive growth of the tumors in syngeneic recipients. (11 Refs)

8. EFFECT OF EPIDERMAL CHALONES ON CELL PROLIFERATION IN REGENERATING EPIDERMIS.

Ketlinskii SA
Lab. Experimental Histology, Inst. Experimental Medicine, Leningrad, USSR
Tsitologiia; 23(7):788-796 1981

The effect of epidermal chalones on proliferative activity of the regenerating epidermis was studied in C57Bl mice subjected to the plucking of hair from the back region. Chalone administration within the first 6 hr after the plucking decreased the fraction of labeled cells. Epidermal cells in G1 phase were less sensitive to chalones. Chalone administration 15 hr after the plucking prevented developme nt of hyperplasia of the epithelial layer. Repeated administration of chalones prior to the plucking inhibited proliferative activity for 25 hr. (30 Refs) (In RUS)

9. GASTRIC POLYPS AND GASTRIC CARCINOMA.

Laxen F
Div. Gastroenterology, Maria Hosp., SF-00180 Helsinki 18, Finland
Ann Clin Res; 13(3):154-155 1981

The association of the different types of polyps with gastric carcinoma and the development of carcinoma from benign polyps were investigated in 363 consecutive cases with endoscopically demonstrated polyp-like lesions. Discrimination between the different groups of adenomas, hyperplastic polyps and foveolar hyperplasia was often difficult; there were numerous transitional forms between the hyperplastic polyps and foveolar hyperplasia. These conditions might be different, morphologically related stages of the same process, which begins as simple hyperplasia of the glands. In some of the patients examined, hyperplastic polyps, polyps of the foveolar hyperplasia type, and inflammatory polyps disappeared spontaneously. It is probable that such polyps are caused by patchily disturbed *cell kinetics* of the foveolar epithelium: the renewal of such cells is more rapid than their destruction. The reversal of the disturbed cell kinetics should theoretically lead to the disappearance of such polyps. Gastric carcinoma was found in 27/363 cases (7.4%): in 38% of adenomas and 6.5% of hyperplastic polyps or foveolar hyperplasia. In 13 of the 27 cases, the gastric carcinomas were found in the gastric mucosa outside the polyps. It is suggested that the entire gastric mucosa should be considered diseased and possessing some malignant potential in the case of non-neoplastic polypoid lesions. (4 Refs)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

10. HUMAN CELL TRANSFORMATION BY SIMIAN VIRUS 40. BIOLOGIC FEATURES OF CLONED LINES.

Sack GH, Obie C
Dept. Medicine, Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Exp Cell Res; 134(2):425-432 1981

Nine lines of doubly cloned Simian Virus 40 transformed human fibroblasts have been isolated. Precrisis in vitro characteristics of growth rate, saturation density, T antigen expression, growth in methylcellulose suspension, protease production and infectious center formation were widely divergent, although distinct for individual lines. Lines with higher T antigen expression had higher growth rates and saturation densities but grew less well in methylcellulose. Chromosome counts in most proliferating lines were in the 38-48 range; one line had 67, whereas another, poorly growing line showed 22. No distinguishing chromosomal abnormalities were present. This biologic heterogeneity suggests distinct molecular differences underlying transformation in the lines and emphasizes the importance of considering various factors as indicative of the transformed state. (Author abstract) (33 Refs)

11. CELL CULTURE STUDIES ON NEUROFIBROMATOSIS (VON RECKLINGHAUSEN) I. COMPARATIVE GROWTH EXPERIMENTS WITH FIBROBLASTS AT HIGH AND LOW CONCENTRATIONS OF FETAL CALF SERUM.

Krone W, Zorlein S, Mao R
Abteilung Humangenetik, Universitat Ulm, P.O. Box 4066, D-7900 Ulm, W. Germany
Hum Genet; 58(2):188-193 1981

Growth experiments were performed to compare the serum requirement and final cell density of fibroblast cultures derived from patients (7 male, 4 female; 13-30 yr old) with neurofibromatosis (NF) with those from 13 healthy donors. Three kinds of primary cultures were set up from NF patients: small minced pieces of skin attached spontaneously to the surface of the culture flask, the skin being derived either from the upper arm or from the immediate vicinity of a neurofibroma; the analogous type of stem culture but with a minced piece of tumor; and finally, collagenase dissociated cells from tumors. The mean ratios of final to initial cell number did not differ significantly between patients and controls, but a high capacity

to grow in media containing 1% or 15% fetal calf serum (fcs) seemed to occur more frequently among NF strains than among control strains. In other experiments, more than three cell population doublings occurred 4x in NF strains and not at all in control strains. A significant difference between NF and control strains occurred only in the 15% fcs series. Higher post-confluent growth potentials occurred more frequently among NF strains than among control strains, although the difference of the frequency of high values reached statistical significance only in the 1% fcs series. In general faster growing strains exhibited lower protein content per cell and the slower higher amounts. The implications of the these findings are discussed. (29 Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

12. MECHANISMS CONTROLLING THE KINETICS IN PROLIFERATION AND DIFFERENTIATION OF POPULATIONS OF MOUSE MYELOID LEUKEMIC CELLS IN VITRO.

Hayashi M, Okabe-Kado J, Hozumi M
Dept. Chemotherapy, Saitama Cancer Center Res. Inst., Saitama 362, Japan
J Cell Physiol; 108(2):123-134 1981

Cells from 2 clones, B24 and DR-3, of mouse myeloid leukemic cell line M1 were grown in a conditioned (CM) medium prepared from Syrian hamster embryo cells. Differentiation of the clone cells was measured at different times and at different concentrations of CM. Differentiation was measured by the ratio of nuclear area to cell area (NCR) and by autoradiographic labeling methods. During cell differentiation the NCR declined from 55% to 10%. Among treated cells those with a high NCR were non-adherent. Those with a low NCR were adherent and had become phagocytic. When cells were grown on CM, and then the CM was removed, some of the cells showed a raised NCR. This suggests that cells which have passed the boundary of about 40-35% are competent to differentiate without CM, while those which have not yet reached this boundary are not. The results suggest that (1) increasing the concentration of CM enhanced the differentiation of the cells and decreases differentiation transit time, (2) the activities of DNA synthesis in individual cells decreased at the stage of cell differentiation at which the NCR was between 30 and 50%, and this decrease was independent of culture time and CM concentration. A stochastic model for the kinetics of proliferation and differentiation of cells simulated the reported observations on the production of differentiated cells. (30 Refs)

13. CLOSE ASSOCIATION OF MOUSE MYELOID LEUKEMIA (M1) CELL DIFFERENTIATION WITH CESSATION OF DNA SYNTHESIS.

Sakagami H, Unten S, Konno K
Dept. Biochemistry, Sch. Medcine, Showa Univ., 1-5-8 Hatanodai, Shinagawa-ku, Tokyo 142, Japan
Cell Struct Funct; 6(2):147-157 1981

Experiments were carried out to determine whether growth retardation in terminally differentiated cells in culture is due to the artefactual production of dead cells or to some intrinsic phenomenon in the cells. Mouse myeloid leukemia M1 cells that had been induced to differentiate in vitro by 10(-6) M dexamethasone (DM) treatment for varying time periods (0-65 hr) were assayed for DNA synthesis by measuring the incorporation of radioactive thymidine into acid-insoluble material. DNA synthesis began to decline after 10 hr of DM treatment and reached one-half the control level after 65 hr; both DM-treated and control cells incorporated approx 20% of the added thymidine initially added to the culture medium and nearly all of this radioactivity was recovered from the acid-soluble fraction, indicating that there is no significant catabolization and reutilization of incorporated label in nonDNA fractions over the time of the experiment; autoradiographs showed that 96.8-98.6% of the label resided in the nucleus. The administration of greater than 10(-4) M arabinofuranosylcytosine inhibited 95% of the thymidine incorporation. The DM-treated cells were fractionated into nonadherent and adherent subpopulations and the adherent cells were gradient-fractionated into further subpopulations based on their density (that reflects the ratio of nucleus to cell size [N/C ratio]). In general, DNA synthesis declined as cell density declined; autoradiographic analysis revealed that this decrease was due to the accumulation of unlabeled cells (cells that cannot carry out DNA replication) with a much lower N/C ratio than the labeled cells. When the distribution of DNA content was measured by flow microfluorometry, the DM-treated cell population contained approx 50% fewer S-phase cells than the untreated population. These results indicate that M1 differentiat ion is closely coupled with the cessation of DNA synthesis. (19 Refs)

14. CONDITIONS REQUIRED FOR THE INHIBITION OF IN VITRO GROWTH OF A MOUSE MYELOMA CELL LINE BY ADHERENT BONE-MARROW CELLS.

Zipori D
Dept. Cell Biology, Weizmann Inst. Science, P.O. Box 26, 76100 Rehovot, Israel
Cell Tissue Kinet; 14(5):479-488 1981

The in vitro growth of the MPC-11 myeloma cell line was inhibited when these cells were co-cultured with adherent cells from mouse bone marrow. This growth inhibition involved prolongation of the specific population doubling time of the MPC-11 cell line. Control cultures of MPC-11 cells exhibited an av doubling time of 14-15 hr, whereas in the presence of adherent layers the length of the doubling time was up to 28 hr. This prolongation in the doubling time did not depend on the duration of incubation, but on the relative proportions of tumor cells and adherent cells employed. MPC-11 cells seeded in relatively high starting cell concentrations partially overcame the growth inhibition. The inhibitory activity of adherent cells from the bone marrow did not appear to be due to production of soluble factor(s), since media conditioned by adherent cells did not affect cell growth. Moreover, in modified cocultures in which MPC-11 cells grew physically separated from the adherent layers, only marginal growth inhibition activity was observed. The possibility that cell-to-cell interactions lead to the inhibition of growth of MPC-11 cells by adherent cells from the bone marrow, and the implications of these findings to the control of cell growth by the hemopoietic microenvironment, are discussed. (Author abstract) (13 Refs)

15. BONE MARROW RESPONSE TO DAMAGE INDUCED BY HYDROXYUREA OR COLCHICINE.

Necas E
DEpt. Pathophysiology, Faculty Medicine, Charles Univ., U nemocnice 5, 128 53 Praha 2, Czechoslovakia
Cell Tissue Kinet; 14(5):537-555 1981

The extent of bone marrow damage caused by the administration of single or repeated doses of either hydroxyurea (1,000 mg/kg body wt) or colchicine (1 mg/kg body wt) are comparable. This conclusion is based on serial studies of bone marrow cellularity and of the CFUc numbers in the bone marrow. The proliferation response of the pluripotential hemopoietic stem cells, determined by the cells forming colonies in the spleen of lethally irradiated mice (CFUs) markedly differs if the bone marrow damage is caused by hydroxyurea or colchicine. While hydroxyurea administration stimulates a large proportion of the *resting G0 cells* into the cell cycle, the damage induced by colchicine is followed by only a mild increase in the CFUs proliferation rate. The seeding efficiency of the spleen colony technique has been determined after both hydroxyurea and colchicine administration. This parameter, important for the est imation of the number of the pluripotential hemopoietic stem cells in blood forming organs, is significantly affected by hydroxyurea administration, but also by repeated injections of colchicine. Following a single dose of hydroxyurea, the time-course of the CFUs numbers, which were corrected for the change in the seeding efficiency, shows an overshoot occurring after 18-20 hr. At the other time periods, the number of pluripotential hemopoietic stem cells is little affected by a single hydroxyurea injection. This poses a question about the nature of the stimulus, which after hydroxyurea administration triggers the CFUs from the resting G0 state into the cell cycle. (Author abstract) (29 Refs)

16. ADRIAMYCIN-ACTIVATED MACROPHAGES AS TUMOR GROWTH INHIBITORS.

Haskill JS
Dept. Obstetrics and Gynecology, Univ. North Carolina, 620, F. L. O. B. Building, Chapel Hill, NC, 27514
Cancer Res; 41(10):3852-3856 1981

Flow cytometry has been used to study the influence of Adriamycin- and Corynebacterium parvum-elicited cytostatic macrophages on the cell cycle of HeLa cells. Macrophages harvested from the peritoneal cavity of mice given ip injections of Adriamycin retain cytostatic activity for 3 to 4 days in vivo. Many of these macrophages fluoresced with the red emission spectra characteristic of Adriamycin. The decline in the presence of macrophages exhibiting red fluorescent cytoplasmic particles paralleled the loss in cytostatic activity. Drug-induced cytostatic macrophages exhibited at least as high a level of growth inhibition as did C. parvum-activated cells. In contrast to the apparent G1 block of HeLa cells which resulted from interaction with C. parvum-activated macrophages, Adriamycin-stimulated macrophages inhibited growth in the G2-M phase characteristic of the free drug. Multiple freeze-thaw cycles removed all activity from C. parvum macrophages but had no influence on the adriamycin-elicited effector cell activity. The data suggest that in vivo drug storage by macrophages may represent an important step in tumor cell destruction by Adriamycin. (Author abstract) (16 Refs)

17. A STUDY OF THE RELATIONSHIP BETWEEN THE MITOTIC ACTIVITY OF CANCER CELLS AND VARIOUS FACTORS OF GASTRIC CANCER PATIENTS.

Tabuchi Y, Takiguchi Y, Murayama Y, Saitoh Y
First Dept. Surgery, Kobe Univ. Sch. Medicine, Ikuta-ku, Kobe 650, Japan
Nippon Geka Gakkai Zasshi; 82(1):42-50 1981

An in vivo stathmokinetic method was used to analyze the mitotic activity of cancer cells from 47 gastric cancer patients. The effect of cellular reaction in cancer tissues on the mitotic activity of cancer cells was examined. The relationship between general factors of the patients such as immunologic activity, changes of protein metabolism and the mitotic activity of cancer cells was also examined. The following results were obtained. An inverse correlation was found between the mitotic activity of cancer cells and the degree of lymphoid cell infiltration in cancer tissues. There was a tendency to a decrease in the mitotic activity of cancer cells paralleling an increase in the degree of delayed skin hypersensitivity to purified protein derivative and phytohemagglutinin and in the number of lymphocytes in peripheral blood. Inverse correlations between the mitotic activity of cancer cells and the values of Hb, hematocrit, albumin and ratio of albumin/globulin were found. Cancer cells showed a tendency to an increase in mitotic activity paralleling an increase in alpha1 and alpha2 globulin of peripheral blood. Highly significant correlations between the mitotic activity of cancer cells and the activity of lactic dehydrogenase (LDH) and its isoenzymes (LDH 3-5) in peripheral blood were observed. These results suggest the possibility that the mitotic activity of cancer cells is regulated by the infiltrating lymphoid cells in cancer tissue and promoted by impairment of cellular immunity. Moreover, it may be estimated that protein metabolism and the function of RBC formation are impaired and that the activity of LDH derived from cancer cells increases in peripheral blood, in parallel with the increase in the mitotic activity of cancer cells. (50 Refs) (In JPN)

CELL CYCLE - SPECIFIC PHENOMENA

18. IMMUNOCYTOCHEMICAL DEMONSTRATION OF INTRACYTOPLASMIC ALKALINE PHOSPHATASE IN HELA TCRC-1 CELLS.

Tokumitsu S, Tokumitsu K, Fishman WH
La Jolla Cancer Res. Foundation, La Jolla, CA, 92038
J Histochem Cytochem; 29(9):1080-1087 1981

The ultrastructural localization of alkaline phosphatase has been examined in cells of a HeLa subline (TCRC-1) that are monophenotypic for Regan isoenzyme expression. Enzyme activity was demonstrated at the cell surface plasma membrane and in certain lysosomes as revealed by the lead citrate method. The regular direct immunoperoxidase procedure utilizing antibodies in IgG or Fab' form showed the same distribution patterns of alkaline phosphatase. However, when the cell surface antigen was blocked in advance with specific unlabeled antibodies and direct immunocytochemistry performed in the presence of saponin, intracellular alkaline phosphatase antigen was observed in the perinuclear space, endoplasmic reticulum, and Golgi apparatus. The results appeared to be concordant with the current concept that membrane glycoproteins are formed in the endoplasmic reticulum, modified in the Golgi apparatus and then transported to the cell surface. Intracellular alkaline phosphatase was observed predominantly in some cell

populations especially mitotic cells, suggesting that the enzyme protein was synthesized in and around the mitotic phase. Accordingly, this technique of differential membrane immunocytochemistry appears to provide an opp ortunity to follow ectopic gene expression as a function of *cell cycle* and enzyme induction. (Author abstract) (28 Refs)

19. GUANINE NUCLEOTIDE DEPLETION AND TOXICITY IN MOUSE T LYMPHOMA (S-49) CELLS.

Cohen MB, Maybaum J, Sadee W
(c/o Sadee) Dept. Pharmacy, Sch. Pharmacy, Univ. California, San Francisco, CA, 94143
J Biol Chem; 256(16):8713-8717 1981

Incubation of mouse T lymphoma (S-49) cells with the inosinate dehydrogenase inhibitor mycophenolic acid produced a depletion of both GTP and dGTP, and resulted in growth inhibition, partial reduction in RNA synthesis, and drastic inhibition of DNA synthesis. Similar results suggested to others that the depletion of dGTP is primarily responsible for toxicity. However, guanosine was as effective as deoxyguanosine at preventing mycophenolic acid toxicity although deoxyguanosine was more effective at elevating dGTP levels. Moreover, in hypoxanthine-guanine phosphoribosyl-transferase-deficient mutants of S-49 (6MPR-3-3) deoxyguanosine was unable to prevent mycophenolic acid toxicity or to re-establish normal DNA synthesis, although it returned cellular dGTP but not GTP levels to normal. No other nucleotide levels changed in a way which could account for the toxicity. Incubation of cells with a combination of deoxyadenosine, deoxycytidine, and erythro-9-(2-hydroxy-3-nonyl)adenine produced a selective depletion of dGTP to levels similar to that produced by mycophenolic acid, but did not affect cell growth. Studies with cells synchronized by centrifugal elutriation show that the toxicity of mycophenolic acid is *specific to the S-phase* of the cell cycle. Addition of actinomycin D at a concentration that inhibited RNA synthesis increased the availability of GTP and re-established normal DNA synthesis in mycophenolic acid-treated S-49 cells. These results suggest that the depletion of GTP rather than that of dGTP produces toxic effects in S-49 cells and that GTP is required for DNA synthesis. (Author abstract) (19 Refs)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

20. SCHEDULE-DEPENDENT SYNERGISM OF COMBINATIONS OF HYDROXYUREA WITH ADRIAMYCIN AND 1-BETA-D-ARABINOFURANOSYLCYTOSINE WITH ADRIAMYCIN.

Ritch PS, Occhipinti SJ, Cunningham RE, Shackney SE
Hematology-Oncology Section, Dept. Medicine, Medical Coll. Wisconsin, 8700 West Wisconsin Ave., Milwaukee, WI, 53226
Cancer Res; 41(10):3881-3884 1981

The lethal effects of combinations of adriamycin (ADR) and either hydroxyurea (HU) or 1-beta-D-arabinofuranosylcytosine (ara-C) were studied in relation to a drug-scheduling interval in Sarcoma 180 cells grown in vitro. Drug lethality was determined by cell cloning in soft agar. Serial kinetic changes induced by a priming dose of HU or ara-C were monitored by flow cytometry and re lated to schedule-dependent cell killing by ADR. All drug exposures were for 1 hr. When ADR was given together with either HU or ara-C, cell log kill was additive. However, when ADR was given after exposure to either HU or ara-C, cell killing was increased up to 200-to 500-fold, respectively. Max schedule-dependent synergism was observed at a drug-scheduling interval of 2 hr; schedule-dependent synergism decreased as the interval between drugs was increased beyond 2 hr. Schedule-dependent synergism was not observed when the same drug combinations were given in reversed order. Drug-induced changes in the DNA histogram were not seen until 5 hr after HU exposure and 8 hr after ara-C exposure. Thus, the schedule-dependent synergism between ADR and either HU or ara-C cannot be explained by cell cycle blockade with synchronization of cells in S phase. (Author abstract) (24 Refs)

21. EFFECT OF MITOMYCIN-C AND ADRIAMYCIN ON CULTURED HUMAN HEPATOMA CELL CYCLE PROGRESSION.

Sano H, Sasaki F, Une Y, Hata Y, Nakanishi Y, Uchino J, Kasai Y
First Dept. Surgery, Hokkaido Univ. Sch. Medicine, Sapporo, Japan
Gan No Rinsho; 27(10):1200-1204,A-57 1981

Eighth generation C-HC-20 cultured human hepatoma cells with a population doubling time of 30.4 hr were separated into individual culture bottles containing 2 x 10(4) cells/2 cc and were treated with mitomycin C (MMC) and/or adriamycin (ADR). Histograms of the cultured cells were made hr 48 and 72 after treatment. On the basis of a standard human dosage of the MMC (4 mg) or the ADR (10 mg), the cells were treated with MMC (20, 2, 0.2, or 0.02 ug/ml) and/or ADR (50, 5, 0.5, or 0.05 ug/ml). Hr 48 after a 1-hr exposure to the MMC, a marked increase in G2-M phase cells were observed with low concentrations of the MMC. Continuous or 1-hr exposure of the cells to the ADR resulted in an increase in G2-M phase cells for up to hr 72 after treatment. On the basis of the results, it was hypothesized that administration of ADR during the 48 hr period after 1-hr administration of low-dose MMC would result in enhanced effects. (17 Refs) (In JPN)

22. EFFECT OF NITIDINE CHLORIDE ON THE LIFE CYCLE OF EHRLICH ASCITES CARCINOMA CELLS IN MICE.

Fan YJ, Zhou J, Li M
Inst. Medical, Pharmaceutical Sci. of Guangni Chuang Autonomous Region, Manning, People's Republic of China
Zhongguo Yaoli Xuebao; 2(1):46-49 1981

Nitidine chloride, an alkaloid isolated from Zanthoxylum nitidum (Roxb) has been shown to have antitumor activities against experimental tumors (eg leukemia L1210 and P388). Using autoradiography, its effect on the cell cycle of Ehrlich ascites carcinoma (EAC) was studied and results are described. The cell cycle time was found to be 38.8 hr. Times for the G1, S, G2 and M periods were 8.0, 25.8, 3.8 and 1.2 hr respectively, with a growth fraction of 0.86. When given ip to EAC-bearing mice, nitidine chloride decreased the mitotic in den and increased the proportion of large-sized EAC cells, indicating a G2 block, but it had no effect on the tritium-TdR pulse labeling index. At 40 mg/kg, nitidine chloride appeared to have killing effects on S cells. It also exhibited significant inhibitory effects on DNA synthesis and lesser effects on RNA synthesis. (7 Refs) (In CHI)

23. CYTOKINETIC AND CYTOTOXIC EFFECTS OF ANTIMETABOLITES ON 9L RAT BRAIN TUMOR CELLS IN VITRO.

Weizsaecker M, Hoshino T, Deen DF, Kobayashi S
(c/o Hoshino) Brain Tumor Res. Center, Univ. California, 783 HSW, San Francisco, CA, 94143
Cancer Res; 41(10):3835-3839 1981

Treatment of exponentially growing 9L monolayer cells with graded concentrations of methotrexate or 5-fluorouracil (5-FU) resulted in approx 95% cell kill, corresponding to the percentage of cells in this system labeled by autoradiography (98%). Additional cell kill could be obtained if 5-FU was administered at a high concentration (7.7 x 10(-4) M) and could be partly reversed in the presence of (8.2 x 10(-5) M) uridine. When cell kill was measured as a function of time of exposure (a 3-hr exposure to 2.2 x 10(-4) M), methotrexate or 7.7 x 10(-6) or 7.7 x 10(-4) M 5-FU killed 30 to 50% of the cell population, which is equivalent to the percentage of the S-phase cells of the system. With both agents, additional cell kill was offset by division of unaffected G2 cells and a drug-induced block of G1 cells at the G1-S border, and it depended on long drug exposure. Nontoxic concentrations of 5-FU could synchronize and increase the fraction of cells in the drug-sensitive S phase. (Author abstract) (19 Refs)

24. INDUCTION OF HYPERPLASIA OF MOUSE EPIDERMIS BY CHOLERA TOXIN.

Kuroki T
Dept. Pathobiochemical Cell Res., Tokyo Univ. Inst. Medical Science, Takanawa, Tokyo 108, Japan
Proc Jpn Acad [B]; 57(3):100-104 1981

Injection of cholera toxin into the dorsal skin of mice was observed to induce two successive synchronous divisions of epidermal cells which resulted in transient hyperplasia without interfering with epidermal differentiation. Stock soln of the cholera toxin was prepared by dissolving it at 1 mg/ml in 0.05 M tris buffer (pH 8.0) containing 50 mg/ml lactose. Immediately before injection, the soln was diluted with cold phosphated buffered saline. Male DDD mice were given intracutaneous injections of 0.1 ml of the diluted soln in four sites in dorsal skin. The mice were sacrificed from 4-6 pm to avoid the complication of possible circadian variation of the epidermal cell cycle. Demecolcine and 3H-thymidine were injected ip 3 hr and 1 hr, respectively, prior to sacrifice. The tissues at the injection sites were examined microscopically and autoradiographically. Intracutaneous injection of the cholera toxin at doses greater than 1.0 nanog evoked an acute reaction at the site of injection. Histologically, mitotic stimulation and hyperplasia of the epidermis and edematous change with granulocyte filtration of the dermis were the most prominent features of the skin lesions. This method was thought to be applicable to two-stage carcinogenesis of mouse skin for the purpose of investigating the possible correlation between epidermal hyperplasia and tumor promotion. (6 Refs)

25. RESPONSE OF EPIDERMAL CELL PROLIFERATION TO ORALLY ADMINISTERED AROMATIC RETINOID.

Fritsch PO, Pohlin G, Langle U, Elias PM
Dept. Dermatology, Univ. Innsbruck, Anichstr. 35, A-6020 Innsbruck, Austria
J Invest Dermatol; 77(3):287-291 1981

Hairless albino mice were fed aromatic retinoid in daily doses ranging from 1 to 50 mg/kg body wt. In animals receiving 1, 5, and 10 mg/kg, the thickness of the epidermis (vertical epidermal cross sectional areas) and the 3H-thymidine labeling indices were determined through a 3-wk observation period. The following additional parameters were determined for animals fed 5 mg/kg; individual and cumulative cross sectional areas of epidermal cell nuclei and cytoplasms, nuclear-cytoplasm ratios, mean epidermal cell vol and mean number of epidermal cells. In animals fed 5 mg/kg for 7 days, an analysis of the cell kinetic parameters was performed including determination of duration of S and G2 phases, mean generation time and the proportion of noncycling (Go) cells. The changes induced by the aromatic retinoid were found to be dose dependent and consisted of a transitory cellular hypertrophy and a persistent numerical hyperplasia linked to increased labeling indices. The mean basal cell generation time was found to be greatly accelerated owing to a ***shortening of all cell cycle phases*** investigated. (Author abstract) (25 Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

26. DNA REPLICATION IN X-IRRADIATED HUMAN LYMPHOCYTES.

Agarwal SS, Katz EJ, Krishan A, Loeb LA
(c/o Loeb) Dept. Pathology SM-30, Univ. Washington Sch. Medicine, Seattle, WA, 98195
Cancer Res; 41(10):3973-3978 1981

Human peripheral blood lymphocytes are well-differentiated cells. Ordinarily, they do not divide and are considered to be in the Go stage of the cell cycle. These cells can be stimulated to undergo DNA replication in culture by mitogens such as phytohemagglutinin. In the present study, we have examined cellular and biochemical events that occur after exposure of lymphocytes to x-irradiation. Irradiation with up to 100 rads, prior to stimulation with phytohemagglutinin, did not interfere with DNA replication. At later periods, DNA replication was inhibited proportional to the amount of radiation. In comparison to DNA synthesis, the effect of x-irradiation on RNA and protein synthesis in phytohemagglutinin-stimu lated lymphocytes was less marked. Furthermore, x-rays did not inhibit either the induction or the continual synthesis of DNA polymerase-alpha or -beta in response to phytohemagglutinin. Kinetic studies with different nucleotide substrates suggest that cellular pools of nucleotides are not significantly altered by x-irradiation. Thus, the inhibition of DNA synthesis in irradiated cells is likely to be due to damage to the cellular DNA template. The inhibition of DNA synthesis was accompanied by accumulation of cells in the G2 and M stages of the cell cycle, suggesting that inhibition of DNA replication by x-irradiation is a postmitotic event. (Author abstract) (38 Refs)

OTHER RELATED STUDIES

27. ALTERATIONS TO CONTROLS OF CELLULAR DNA SYNTHESIS BY ADENOVIRUS INFECTION.

Braithwaite AW, Murray JD, Bellett AJ
Dept. Microbiology, John Curtin Sch. Medical Res., Australian Natl. Univ., Canberra, A.C.T., 2601, Australia
J Virol; 39(2):331-340 1981

Human adenovirus type 5 and temperature-sensitive mutants ts36, ts37, and ts125 induced cellular DNA synthesis in quies-

cent rodent cells at both permissive and nonpermissive temperatures. Cellular DNA synthesis induced by adenovirus type 5 or by serum required protein synthesis for both initiation and continuation, whereas viral DNA synthesis was not dependent upon continued protein synthesis once it was initiated. Both cellular and viral DNA replication was induced in adenovirus type 5-infected cells in the presence of dibutyryl cyclic AMP at concentrations which inhibited induction by serum, which suggested that some of the controls of DNA synthesis in serum-treated and virus-infected cells are different. After adenovirus infection of quiescent cells, there was a decrease in the number of cells with G1 DNA content and an increase in cells with G2 diploid and greater DNA contents. Thus, adenovirus type 5 induces a complete round of cellular DNA replication, but in some cells, it induces a second round without completion of a normal mitosis. These results suggest that adenovirus type 5 is able to alter cell growth cycle controls in a way which may be related to its ability to transform cells. (Author abstract) (32 Refs)

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KINETIC METHODS AND MODELS

1. SEPARATION OF HUMAN BONE MARROW CELLS BY SEDIMENTATION.

Guerci O, Huot-Marchand F, Schneider O
Maison Hospitalier, Saint-Charles 56, rue des Quatre-Eglises, F-5400 Nancy, France
Scand J Haematol; 26(5):378-384 1981

Sedimentation at unit gravity of human bone marrow cells, for 15 hr at 4 C on a linear density gradient of Ficoll in culture medium ranging from 1.020 to 1.065 g/ml shows that a differential migration of the bone marrow cell sub-populations exists with precise mean densities 1.021 +-! x 10(-3) g/ml for lym-

HE 20.3173/2:

phocytes; 1.024 +-2.5 x 10(-3) g/ml for non-eosinophil granulocytes; 1.025 +-2.5 x 10(-3) g/ml for metamyelocytes; 1.030 +-3.5 x 10(-3) g/ml for other myeloid cells (myeloblasts, promyelocytes, myelocy tes); 1.040 +-3 x 10(-3) g/ml for eosinophil granulocytes; and 1.055 +-10 x 10(-3) g/ml for megakaryocytes. The highest percentages of S phase cells and G2 and M phase cells determined by a cytofluorograph correspond to the peaks of immature myeloid cells (myeloblasts, promyelocytes and myelocytes). This method of bone marrow cell separation may be used to study the cell cycle in pathological bone marrows (leukemia in particular) and to determine the effects and the efficiency of some antimitotics. (Author abstract) (14 Refs)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

2. A FLOW CYTOMETRIC DEOXYRIBONUCLEIC ACID ANALYSIS OF PAPILLARY THYROID CARCINOMA.

Johannessen JV, Sobrinho-Simoes M, Tangen KO, Lindmo T
Dept. Pathology, Norwegian Radium Hosp., Montebello, Oslo 3, Norway
Lab Invest; 45(4):336-341 1981

We present the first comprehensive flow cytometric analysis of papillary carcinoma of the human thyroid. All but 1 of the 22 papillary carcinomas showed a unimodal distribution of the nuclear DNA content. The mean modal DNA was significantly lower in papillary carcinomas than in normal thyroid tissue, a finding which is contradictory to some earlier reports based on conventional cytophotometry. Tumors predominantly composed of Hurthle cells had a significantly higher mean modal DNA, whereas no significant difference was found between tumors with many ground glass nuclei and those lacking this nuclear feature. A very low percentage of S-phase cells was found both in the primary tumors and their metastases. This percentage was even lower than in normal thyroid tissue. The low proliferative activity may in part explain why most papillary thyroid carcinomas run such a surprisingly indolent course even after the establishment of regional lymph node metastases. (Author abstract) (34 Refs)

3. GROWTH KINETICS.

Alison MR, Wright NA
Dept. Histopathology, Royal Postgraduate Medical Sch., Hammersmith Hosp., Ducane Road, London W12 OHS, England
Recent Results Cancer Res; 78:29-43 1981

Since direct estimates of growth rate of prostate cancer (PC) are unfeasible in humans, the respective roles of cell production and cell loss in determining overall tumor growth rates can only be speculative. The mitotic rate and thymidine labeling, DNA analysis of cells in tumors, studies in culture, and experimental prostatic tumors are each discussed.The mitotic index data suggest that some of the more poorly differentiated tumor types have higher cell production rates than the majority of moderately to well-differentiated tumors. Most experimental tumors grow faster than those in man. The slow growth rate of human tumors indicates the presence of important growth restraints. Mitotic Rate and thymidine labeling and studies in tissue culture of benign prostatic hyperplasia are discussed. Androge ns and the cell cycle are discussed with respect to the growth fraction, stimulated DNA synthesis, and some properties of stimulated cells. In populations with a low proliferative rate it may be difficult to distinguish between cells slowly progressing through the division sequence and those cells actually arrested or resting in a separate phase (G0). Evidence is presented that most cells in prostatic tissues are in a state of proliferative rest (G0), and that increased cell production is achieved by actively promoting G0 cells into the division sequence. (49 Refs)

4. IN VIVO AND IN VITRO GROWTH OF A RAT TRACHEAL SQUAMOUS CELL CARCINOMA.

Tennyson GS, Lane BP
Dept. Pathology, Health Sciences Center, State Univ. New York, Stony Brook, NY, 11794
Cancer Res; 41(11,part1):4687-4692 1981

We investigated the effect of in vitro and in vivo environments on the growth behavior of two stable, related rat tracheal squamous cell carcinoma lines while controlling for cell selection. One line was transplanted as tumors in syngeneic hosts for 2 yr of continuous passage, and the other was derived from an early tumor passage and maintained continuously in cell culture. The in vitro cell cycle kinetics and doubling time of cells from the transplanted tumor line were identical to those of the long-term-cultured cell line and, when implanted into syngeneic hosts, the cultured cell line gave rise to tumors with growth behavior that was the same as that of the transplanted tumors. The differences in the cell cycle kinetics and growth parameters of the cells in the solid tumors and of the same cells in culture can be explained on the basis of differences in their environments. Selection for different populations of cells when the cells are transferred between environments is unlikely. The comparability of the populations in each of the two environments supports the validity of tests on cells isolated from solid tumors, as long as the cells are simply transferred between the environments and are not allowed to undergo selection during passage in the new environment. (Author abstract) (32 Refs)

5. REVERSIBLE INHIBITION OF RAT HEPATOCYTE PROLIFERATION BY HYDROCORTISONE AND ITS EFFECT ON CELL CYCLE-DEPENDENT HEPATOCARCINOGENESIS BY N-METHYL-N-NITROSOUREA.

Kaufmann WK, Kaufman DG, Rice JM, Wenk ML
(c/o D. Kaufman) Dept. Pathology, Sch. Medicine, Univ. North Carolina, Chapel Hill, NC, 27514
Cancer Res; 41(11,part1):4653-4660 1981

The susceptibility of hepatocytes to carcinogenesis in vivo may be influenced by the phase of the cell cycle at which carcinogen-induced damage is incurred. In order to better understand this relationship, hepatic cell proliferation in juvenile male Fischer 344 rats was charted following a two-thirds partial hepatectomy. For hepatocytes, two distinct waves of DNA synthesis occurred which were followed af ter 6 to 8 hr by waves of mitotic cell division. In contrast to this kinetic pattern, when hydrocortisone was given after the partial hepatectomy, the initial waves of DNA synthesis and mitosis by hepatocytes were each delayed by about 15 hr. In rats not given hydrocortisone, susceptibility to hepatocarcinogenesis by N-methyl-N-nitrosourea was greatest at 20 hr after partial hepatectomy when the peak fraction of proliferating hepatocytes was in the S phase. By shifting the time of onset of DNA synthesis, the hydrocortisone treatments also shifted the time with greatest sensitivity to N-methyl-N-nitrosourea, with hepatocytes in late G1 or S again the most susceptible. Numerous tumors were also induced by N-methyl-N-nitrosourea in extra-

hepatic tissues, including intestine, Zymbal's gland, nervous system, kidney, odontogenic tissues, and peritesticular mesothelium. The results illustrate the importance of cell proliferation in carcinogenesis and further point to the specific sensitivity of certain cell cycle phases. (Author abstract) (31 Refs)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

6. GROWTH CHARACTERISTICS OF HUMAN GLIOMA-DERIVED AND FETAL NEURAL CELLS IN CULTURE.

Icard C, Liepkalns VA, Yates AJ, Singh NP, Stephens RE, Hart RW (c/o Yates) Dept. Pathology, Neuropathology Unit, Ohio State Univ., 473 West 12th Ave., Columbus, Ohio, 43210
J Neuropathol Exp Neurol; 40(5):512-525 1981

Growth characteristics of human fetal neural cells (CH) and human glioblastoma multiforme-derived cells (12-18) in culture were compared. Cells were grown to confluent densities of 38,000 to 42,500 cells/cm2 for CH and 85,800 to 87,100 for 12-18. Population doubling times were 40.0 +-5.1 hr and 66.5 +-9.8 hr for CH and 12-18 cells, respectively. The mean DNA content per cell of the glioma-derived cells was twice that of the fetal brain cells at sparse, log, and confluent cell densities. High concentrations (40%) of serum in growth medium increased DNA contents in confluent CH, but not 12-18, cells. The amount of protein per cell also was consistently higher in glioma cells than CH cells, but, as cell densities increased, protein contents decreased for both: 1200 to 700 pg/cell in glioma cells, and 840 to 560 pg/cell in CH cells. In each cell line, initial rates of [3H]ThdR incorporation into TCA precipitable material decreased as cell density increased, but confluent glioma-derived cells incorporated 10x more [3H]ThdR than confluent fetal cells. Almost all CH cells had a normal diploid chromosome number of 46. A histogram showing the relative frequencies of chromosome numbers of glioma-derived cells had peaks of 52, 79, and 105 chromosomes per metaphase, indicating a haploid number of 26 for most cells. Lengths of cell cycle phases, determined using autoradiographic techniques, indicate that glioma-derived cells had a longer gen eration time and S period than fetal neural cells. These data demonstrate several biological differences between glioblastoma-derived cells and non-neoplastic fetal neural cells, indicating that this system is of potential value for comparative studies on growth control and contact inhibition. (Author abstract) (31 Refs)

7. CHARACTERIZATION OF HUMAN CELLS TRANSFORMED BY CHEMICAL AND PHYSICAL CARCINOGENS IN VITRO.

Milo GE, Oldham JW, Zimmerman R, Hatch GG, Weisbrode SA Dept. Physiological chemistry, Coll. Medicine, Ohio State Univ., 333 W. 10th Ave., Columbus, OH, 43210
In Vitro; 17(8):719-729 1981

Several different classes of chemical carcinogens induced the transformation of human fibroblasts grown in vitro. Characteristics of the events that occur from time of treatment through the expression of neoplastic transformation are presented. The S-phase appeared to be the portion of the cell cycle most vulnerable to insult. Staging of the cells by blocking them in G1 before releasing them to proceed through scheduled DNA synthesis (S) was required to induce reproducible transformation. Compounds such as insulin were added to the cells upon release from the block to sensitize the cells to the carcinogen that was added during S. Growth of the transformed cells as distinct from nontransformed cells was promoted by growth in medium supplemented with 8X nonessential amino acids. Carcinogen-treated cells in the early stage of transformation exhibited abnormal colony morphology and were able to grow at 41 C, in air atmosphere, and in medium supplemented with only 1% serum. In addition, the transformed cells were insensitive to KB cell lysate and exhibited density independent, as well as anchorage independent, growth (ie, growth in 0.33% agar). Cells that grew in soft agar also produced undifferentiated mesenchymal tumors in preirradiated nude mice. (Author abstract) (19 Refs)

8. LUTROPIN RECEPTORS IN NORMAL AND TUMOUR LEYDIG CELLS.

Cooke BA, Dix CJ, Magee-Brown R Dept. Biochemistry and Chemistry, Royal Free Hosp. Sch. Medicine, Univ. London, 8 Hunter St., London WC1N 1BP, England
Biochem Soc Trans; 9(1):40-42 1981

Leydig cells from normal adult mouse and rat testes and a Leydig cell tumor can be separated into two cell populations (both containing lutropin receptors) which differ in density and steroidogenic responsiveness. The etiology of these cell types is unknown. They may reflect different ***phases in a cell cycle.*** Treatment with gonadotropin (lutropin or human choriogonadotropin) in vivo has been shown to result in the loss of lutropin receptors, a reduction in adenylate cyclase activity, and reduced steroidogenesis; treatment of rats with gonadotropin results in reduced sensitivity of Leydig cells to lutropin in vitro. Tumor cells of density 1.07 g/ml were exposed in vitro to lutropin (0.0, 10, 100, or 1,000 nano g/ml) and exhibited an initial increase in number of lutropin receptors. This reached a max in the controls after 2 hr and remained constant thereafter. All lutropin-treated cells showed decreased binding of choriogonadotropin after 1-2 hr incubation. Basal production of cyclic AMP initially reflected pretreatment with lutropin. Cyclic AMP rose sharply within 1 hr and returned to normal pretreatment levels by 4 hr. Reduction in binding of choriogonadotropin was inhibited by cycloheximide, which prevented lutropin-induced desensitization of adenylate cyclase activity. Results indicate that desensitization of Leydig cells can be induced in vitro, and loss of both lutropin receptors and adenylate cyclase activity occurs simultaneously; both processes depend on protein synthesis. (16 Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

9. THE RELATIONSHIP BETWEEN LYMPHOCYTE NUCLEAR MORPHOLOGY AND CELL CYCLE STAGE IN LYMPHOID NEOPLASIA.

Diamond LW, Weisenburger DD, Rappaport H Dept. Pathology, Temple Univ. Sch. Medicine, Philadelphia, PA, 19140
Am J Hematol; 11(2):165-173 1981

A significant percentage of lymphoid cells isolated from three lymphoid neoplasms (nodular lymphoma mixed cell type, mycosis fungoides, and Sezary syndrome) had tetraploid or near-tetraploid DNA content, as determined by flow cytometric analysis. In each case, a morphologically distinct population of cells with large, irregular nuclei was present, the per-

centage of which corresponded to the percentage of tetraploid cells. In a fourth case (diffuse 'histiocytic' lymphoma), cells were sorted on the basis of DNA content from the G0-G1 compartment and compared morphologically to cells sorted from the S-G2 (M) compartment. The G0-G1 cells had clumped nuclear chromatin, lacked prominent nucleoli, and had a mean nuclear diameter of 10.18 +-1.22 um. The sorted cells with S-G2(M) DNA content had one to several prominent nucleoli and less clumped nuclear chromatin, and they were significantly larger, with a mean nuclear diameter of 13.76 +-1.59 um (p less than 0.00001). These preliminary results suggest that, in lymphoid malignancies, certain morphologic characteristics of individual lymphoid cells are related to their DNA content (level of ploidy) and/or the stage of the cell within its division cycle. (Author abstract) (18 Refs)

10. EPIDERMAL CELL (KERATINOCYTE)-DERIVED THYMOCYTE-ACTIVATING FACTOR (ETAF).

Luger TA, Stadler BM, Katz SI, Oppenheim JJ
NIH, Natl. Inst. Dental Res., Bldg. 30, Room 324, Bethesda, MD, 20205
J Immunol; 127(4):1493-1498 1981

In order to determine whether keratinocytes play a role in the modulation of the immune response, we investigated the murine keratinocyte cell line Pam 212. In culture these cells generate a substance with a biologic activity that greatly enhances phytohemagglutinin-induced thymocyte pro liferation. We have, therefore, called this substance epidermal cell thymocyte-activating factor (ETAF). This keratinocyte-derived supernatant activity is mainly produced at the onset of the ***logarithmic growth*** phase and is directly mitogenic for murine thymocytes. Although ETAF by itself exhibits no T cell growth factor activity, ETAF enhances interleukin 2 production by mitogen-stimulated murine spleen cells. Murine ETAF is not genetically restricted and lacks species specificity since it decreases lectin-induced proliferation of human peripheral blood lymphocytes (as well as murine spleen cells) and also enhances the production of human interleukin 2. The factor has a mol wt between 15,000 and 25,000 as determined by gel filtration and elutes as a single peak from anion exchange chromatography columns. The activity is maintained mainly at alkaline pH and is rapidly destroyed at temperatures above 60 C. These observations suggest that epidermal cells may interact with the immune system by elaborating nonspecific factors that modulate lymphocyte proliferation and augment lymphokine production. (Author abstract) (41 Refs)

CELL CYCLE - SPECIFIC PHENOMENA

11. S PHASE-SPECIFIC SYNTHESIS OF DIHYDROFOLATE REDUCTASE IN CHINESE HAMSTER OVARY CELLS.

Mariani BD, Slate DL, Schimke RT
(c/o Schimke) Dept. Biological Sciences, Stanford Univ., Stanford, CA, 94305
Proc Natl Acad Sci USA; 78(8):4985-4989 1981

We investigated the cell cycle modulation of dihydrofolate reductase (DHFR; tetrahydrofolate dehydrogenase, 7,8-dihydroxyfolate: NADP+ oxidoreductase, EC 1.5.1.3) levels in methotrexate-resistant Chinese hamster ovary cells synchronized by mitotic selection. DNA content and DHFR concentration were analyzed throughout the cell cycle by standard biochemical techniques and by double fluorescence staining utilizing the fluorescence-activated cell sorter. We found an S phase-specific period of DHFR biosynthetic activity. Commencing within hr 2 of S phase and continuing throughout the duration of S phase, there is a 90% increase in DHFR specific activity. This results from an approx 2.5-fold increase in the level of DHFR, while total soluble protein increases 50% during the same period. This increase is the result of new synthesis of DHFR molecules initiated after the cell is physiologically committed to DNA replication. This increase in DHFR activity through S phase parallels the increasing rate of [3H]thymidine incorporation during the same interval. The max peak of DHFR activity is coincident with the max rate of DNA synthesis, both activities occurring during the bulk of DNA replication within the last stages of the 6.5-hr phase. (Author abstract) (26 Refs)

12. RIBONUCLEOTIDE REDUCTASE IN CULTURED MOUSE LYMPHOMA CELLS. CELL CYCLE-DEPENDENT VARIATION IN THE ACTIVITY OF SUBUNIT PROTEIN M2.

Eriksson S, Martin DW
Howard Hughes Medical Inst. Lab., Univ. California, San Francisco, CA, 94143
J Biol Chem; 256(18):9436-9440 1981

Ribonucleotide reductase is responsible for the production of the deoxyribonucleotides required for DNA synthesis. The enzyme is composed of two dissociable subunits, proteins M1 and M2, which are inactive alone, but are fully active when combined. From mouse S49 T lymphoma cells we have isolated and separated the two subunits and used each for determining the activity of the complementary subunit in extracts from cells of different phases in the cell cycle. Treatment of S49 cells with cAMP analogs (eg Bt2cAMP) results in the protein kinase-dependent arrest of the cells in the G1 phase of the cell cycle. Ribonucleotide reductase (holoenzyme) activity fell in S49 cells treated for more than 16 hr with Bt2cAMP but was unchanged during short term treatments. The activity of protein M2 was decreased in parallel to the overall activity of ribonucleotide reductase, while protein M1 activity changed less. Removal of Bt2cAMP after 24 hr exposure resulted in increased holoenzyme and protein M2 activities. Centrifugal elutriation of exponentially growing S49 cells separated cells into a 90% pure G1 cell population, a mixture of G1 and early S phase cells and a 95% pure S phase/G2 cell population. The specific catalytic activity of protein M1 was the same in all these fractions while that of protein M2 was decreased 60% in the G1 cell population. These results demonstrate that the ribonucleotide reduction necessary for DNA synthesis is regulated in a cell cycle-dependent fashion by the activity of the protein M2 subunit of ribonucleotide reductase. (Author abstract) (32 Refs)

13. EFFECTS OF 1-BETA-D-ARABINOFURANOSYLCYTOSINE ON CHROMOSOMES, DEPENDING UPON THE CELL CYCLE STAGE AT THE TIME OF EXPOSURE.

Moore RC
Biological Res. Unit, Cancer Inst., 481 Little Lonsdale St., Melbourne 3000, Australia
Mutat Res; 83(3):361-374 1981

JU56 cells, derived from the black-tailed wallaby, were exposed to 1-beta-D-arabinofuranosylcytosine (ara-C), and the frequencies and types of chromosomal aberrations were scored

in samples of c-metaphase cells collected at consecutive intervals throughout and following the cell cycle, under conditions which prevented cells in their second division following treatment from being included in the samples scored. For cells exposed in G2, both chromatid-type and chromosome-type lesions were observed. A chase with deoxycytidine (CdR) reduced the frequency of these lesions. There was some evidence that the initial lesions were gaps that may later have been converted into true chromosomal breaks. Lesions were produced chiefly at one chromosome location in early G2 and late S cells; the location was not specifically late-replicating. In all samples of cells in S at the time of exposure to ara-C, aberrations were chiefly, but not entirely, of the chromatid type; there was some evidence that their frequency was correlated with the ratio of DNA synthesis in the affected cells at the time of exposure to the drug. G1 cells were not susceptible to damage of ara-C. The level of damage in S cells was not affected by CdR chase. At no stage in the cell cycle did the lesions observed with ara-C imitate those produced by x-rays. (18 Refs)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

14. FLOWCYTOMETRIC ANALYSIS OF THE EFFECT OF ANTITUMOR DRUGS USING A HUMAN NEUROBLASTOMA MODEL XENOGRAFTED INTO NUDE MICE.

Tsuchida Y, Yokomori K, Saito S, Takakura K, Yamamoto H, Nomura K
Dept. Pediatric Surgery, Faculty Medicine, Univ. Tokyo, Bunkyo-ku, Tokyo 113, Japan
Shoni Geka; 13(4):517-524 1981

Nude mice bearing human neuroblastoma in the sc tissue were injected ip with cis-platinum 10 mg/kg mouse wt, and changes in the cell cycle of the tumor specimens were studied with flow-cytometry. An increase in S phase cells and in G2 + M phase cells occurred 24-48 hr and 72 hr after the injection, respectively. Nude mice bearing human neuroblastoma were treated more effectively when epipodophyllotoxin was given 72 hr after the treatment with cis-platinum, or when adriamycin was given 36 hr after the treatment with cis-platinum, than when they were treated with the single agent alone. A significant increase in S phase was observed 7 days after subtotal resection of the tumor mass, and adriamycin given 7 days postoperatively was found more effective than that given 14 days postoperatively. (10 Refs) (In JPN)

15. IN VIVO CELL CYCLE PHASE-PREFERENTIAL KILLING OF MURINE FIBROSARCOMA CELLS BY CISPLATIN.

Sigdestad CP, Grdina DJ
Therapeutic Radiology Dept., Univ. Louisville, Radiation Center, 500 S Floyd St., Louisville, KY, 40292
Cancer Treat Rep; 65(9):845-851 1981

Fibrosarcoma cells were separated by centrifugal elutriation. Selected populations enriched in G1-, S-, or G2 + M-phase cells were then injected (10(4) cells) into the tail veins of C3Hf/Kam mice. Twenty min later, 4 mg/kg of cisplatin was injected iv into one half of the animals in each experimental group. Fourteen days later the number of lung colonies was scored, and the surviving fractions were plotted against the elutriator fraction numbers. The results indicated that all phases of the cell cycle were sensitive to cisplatin but that the G1 phase was the most sensitive by a factor of 10. Biphasic dose-response curves were observed for unseparated control, S-phase, and G2 + M-phase tumor cell populations, indicating a resistant cell population. G1 cells, however, had log killing over four decades without the resistant tail. Using this in vivo system, it is concluded that cisplatin kills cells throughout the cell cycl e but exhibits preferential killing of G1 tumor cells. (Author abstract) (26 Refs)

16. DIFFERENTIAL RESPONSE OF ELUTRIATED 9L CELLS TO TREATMENT WITH 1,3-BIS(2-CHLOROETHYL)-1-NITROSOUREA.

Hoshino T, Deen DF, Williams ME, Sano Y
Brain Tumor Res. Center, Dept. Neurological Surgery, Sch. Medicine, Univ. California, San Francisco, CA, 94143
Cancer Res; 41(11,part1):4404-4407 1981

Earlier cytokinetic studies using 9L monolayer culture cells showed that cells began accumulating in the G2 phase (4C position in the DNA distribution) within 30 hr after administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml). Most of these cells reached the G2 phase at 48 hr and remained there for another 24 hr. Similar studies using 9L spheroid culture cells show that 9L cells also began to accumulate at the 4C DNA position 30 hr after administration of 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml); however, only one-half of the cells accumulated in the 4C peak during the first 48 hr after treatment, while the other half remained at the 2C position. Those that remained at the 2C peak might correspond to the G0 cells that exist in 9L spheroids. When one-half the cells were in 2C and one-half were in 4C, the spheroids were dissociated using an enzyme cocktail and sorted using centrifugal elutriation. Cells from each elutriated fraction were analyzed for DNA content using flow cytometry and for viability using a colony-forming efficiency assay. Results indicated that in spheroids, 1,3-bis(2-chloroethyl)-1-nitrosourea (3 ug/ml) is more effective against noncycling cells and that repopulation is more vigorous in G2-arrested cells, which presumably were cycling at the time of treatment. (Author abstract) (24 Refs)

17. EFFECTS OF RETINOIDS ON KERATINOCYTES IN VITRO.

Mahrle GO, Wilkinson DI, Farber EM
Universitats-Hautklinik, Von-Siebold-Strasse 3, D-3400 Gottingen, W. Germany
Retinoids: Advances in Basic Research and Therapy, Proceedings of the International Dermatology Symposium held in Berlin, W. Germany, 13-15 October, 1980. Orfanos CE, Braun-Falco O, Farber EM, Grupper C, Polano MK, and Schuppli R, ed. Berlin, Springer-Verlag, 527 pp., 1981.

In tests on guinea pig epidermal cells in vitro vitamin A acid (VAA) stimulated cell growth and protein synthesis and increased the absolute and relative numbers of attached cells during the replicative and proliferative phases. VAA promoted detachment of cells during the plateau phase of cell growth. The aromatic retinoid Ro 10-9359 had little or no such effects. (20 Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

18. SELECTIVE MODIFICATION OF THE X RAY SURVIVAL RESPONSE OF TWO MOUSE MAMMARY ADENOCARCINOMA SUBLINES BY N,N-DIMETHYLFORMAMIDE.

Leith JT, Brenner HJ, DeWyngaert JK, Dexter DL, Calabresi P, Glicksman AS
Brown Univ., Box G, Providence, RI, 02912
Int J Radiat Oncol Biol Phys; 7(7):943-947 1981

The effects of the polar solvent N,N-dimethylformamide (DMF) on the radiation sensitivities of two mouse mammary adenocarcinoma tumor cell sublines (lines 66 and 67) were studied. Treatment with 0.2% DMF had no effect on the cell growth rate as compared to untreated control flasks. For line 66, 0.5% DMF increased the cell culture doubling time to about 25.3 hr, and 0.8% DMF increased the doubling time to about 27.0 hr, which amounted to increases of about 18% and 27%, respectively. For tumor subline 67, 0.5% DMF also did not significantly change the cell culture doubling time. However, the 0.8% DMF concentration did increase the cell culture doubling time to about 28.7 hr, an increase of about 22%. The postirradiation survival of line 66 was markedly reduced by the treatment with 0.8% DMF. This effect was predominantly a result of a reduction by about 70% in the 'shoulder' region of the survival curve. In contrast, treatment with DMF affected the postirradiation survival of line 67 less drastically (37%). The predominant effect of DMF was on the initial slope, with line 66 being significantly more affected than line 67. The results indicated that DMF increased radiation sensitivity but reduced the variability in radiation response between heterogeneous tumor cell sublines. (24 Refs)

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KINETIC METHODS AND MODELS

1. CYCLE CYCLE KINETICS OF IRRADIATED SYNCHRONOUS AND ASYNCHRONOUS TUMOR CELLS WITH DNA DISTRIBUTION ANALYSIS AND BRDURD-HOECHST 33258-TECHNIQUE.

Nusse M
Abteilung fur Biophysikalische Strahlenforschung, Gesellschaft fur Strahlen- und Umweltforschung, Paul-Ehrlich-Strasse 15, Frankfurt/M, W. Germany
Cytometry; 2(2):70-79 1981

The recently developed BrdUrd (bromodeoxyuridine) substitution method was employed in the study of effects of x-irradiation (4 Gray) on the perturbation of cell cycle phases in asynchronous and synchronous Ehrlich ascites tumor cells (EATC). Radiation-induced progression delay in S-phase and G 2-block, depending on time of irradiation in the cell cycle, were measured in synchronized EATC in vitro using flow cytometric analysis of DNA in single cells. Similar results could be obtained with the BrdUrd-Hoechst technique after irradiating asynchronous cells. In this technique BrdUrd replaces thymidine in newly synthesized DNA which does not stain with the thymidine-specific dye Hoechst 33258. Temporal development of fluorescence distribution after addition of BrdUrd was measured by flow cytometry. In asynchronous cells mean durations of the cell cycle phases and their perturbations after irradiation could be calculated, and the data agreed with results in synchronized cells. Division delay consisted of a small progression delay in S-phase and block in G2-phase. Both effects depended on time of irradiation during the cell cycle with delay in S-phase increasing in irradiated late S-cells and G2-block increasing in irradiated G2-cells. Model calculations showed that results of both types of experiments were consistent and complemented each other. (38 Refs)

2. PHARMACOKINETICS OF VINBLASTINE IN RAT BLOOD PLASMA AND TUMOUR TISSUE DETERMINED BY A BIOLOGICAL METHOD USING FLOW CYTOFLUORIMETRY.

Kipp JB, Barendsen GW
Lab. Radiobiology, Univ. Amsterdam, Plesmanlaan 121, 1066 CX Amsterdam, The Netherlands
Eur J Cancer Clin Oncol; 17(8):867-873 1981

For the optimal use of vinblastine as an antineoplastic agent, knowledge of the pharmacokinetic distribution in blood plasma and tumor tissue is necessary. A method is presented for the determination of mitotic inhibitory activity of vinblastine and its metabolites, extracted from tissue samples. With this method concentrations as low as 0.005 mg/l which are biologically active can be reproducibly determined. The method has been applied to follow the concentration of vinblastine in blood plasma and tumor tissue after injection of 1.5 mg of vinblastine/kg body wt in WAG/Rij rats with a R-1,M tumor of 0.3-1.0 g growing in the flank. The high concentration in plasma immediately after iv injection decreases quickly within 24 hr to the minimal detectable concentration in plasma of 0.01 mg/1. Although after ip injection the concentration in plasma is lower initially, at 24 hr it tends to be higher than after iv injection. In tumor tissue the max concentration is reached at 6 hr after iv injection (3.0 mg/kg) and at 12 hr after ip injection (0.6 mg/kg). From 12 hr after ip injection the concentration remains constant during 2-3 days while after iv injection a slow decrease is observed. These pharmacokinetic data are compared with the changes of cell proliferation kinetics in the tumor induced by vinblastine. The finding that after iv injection the max concentration in tumor tissue is higher and is reached earlier than after ip injection correlates well with the higher degree of accumulation of cells in mitosis. (Author abstract) (13 Refs)

3. SOLID KHT TUMOR DISPERSAL FOR FLOW CYTOMETRIC CELL KINETIC ANALYSIS.

Pallavicini MG, Folstad LJ, Dunbar C
Lawrence Livermore Natl. Lab., Univ. California, P.O. Box 5507 L-452, Livermore, CA, 94550
Cytometry; 2(2):54-58 1981

A neutral protease (NP) from Bacillus polymyxa was evaluated for usefulness in dispersal for cell kinetic studies of unperturbed and perturbed KHT tumors in comparison with use of a trypsin/DNase (T/D) procedure. NP-dispersed tumors yielded approx 4x more cells than those dispersed with T/D with approx a 1.5-fold higher plating efficiency on semisolid agar. Untreated and cytosine arabinoside-perturbed tumors dispersed by both procedures yielded the same quantitative DNA distribution analyses. The rate of incorporation of (H3)thymidine in mice bearing the KHT tumor was lowest in early S-phase and approx 4-fold greater in late S-phase, with no significant differences between the two dispersal procedures. Preferential phase-specific cell loss was not observed with either NP or T/D. NP provides good single cell suspension of KHT tumor for cell survival measurements and for cell kinetic analysis of drug-induced perturbations. The high cell yields with use of NP facilitate electronic cell sorting, especially where large numbers of cells may be required. (14 Refs)

4. MULTIPARAMETER FLOW CYTOMETRY. PART I: APPLICATION IN ANALYSIS OF THE CELL CYCLE.

Darzynkiewicz Z, Andreef M
Sloan-Kettering Inst., New York, NY
Clin Bull; 11(2):47-57 1981

Application of multiparameter flow cytometry to study of the cell cycle is reviewed. Techniques designed to measure other cell features in addition to DNA content are specific for RNA content and simultaneous DNA and RNA content, detection of incorporated 5-bromodeoxyuridine, and analysis of nuclear chromatin structure. (56 Refs)

5. CELL GROWTH FACTOR ACTIVITY: NEW QUANTITATIVE METHOD IN CELL CULTURE ASSAY.

Chen CH, Chen SC
Biochemistry Lab., Wilmer Ophthalmological Inst., Johns Hopkins Univ. Sch. Medicine, Baltimore, MD, 21205
Exp Cell Res; 136(1):43-51 1981

This quantitative method for the assay of growth factor activity in vitro was developed empirically. Based on the empirical equations, it seems logical to express the cell growth rate by cell duplication frequency, f, and the growth factor activity by the normalized cell growth rate: 1/(T-Tmin). The latter is recommended as the basis of defining an arbitrary unit of growth factor activity. For the in vitro growth factor activity assay, the quantitative method based on the empirical equations has two important features: (1) it appears to express linearly the growth factor concentration in assay, and (2) it is not affected by the initial cell counts and the length of cultivation. The view that these two features overcome the apparent defects associated with the expression systems that use the cell count ratio and net cell count is discussed. The quantitative method based on the empirical equations has been verified with

experiments and compared with expression systems using the cell count ratio and net cell count. The experiments, which verified the quantitative method based on the empirical equations, were carried out with four selected cell lines: aortic endothelial cells, mouse 3T3 fibroblasts, Walker 256 carcinoma, and Chang's liver cells, using serum as the source of growth factor(s) for all cell lines. Vitreous, retinal extract, and Walker 256 carcinoma extract were also used for aortic endothelial cells. (Author abstract) (24 Refs)

6. SEPARATION OF NORMAL HEMOPOIETIC STEM CELLS FROM CLONOGENIC LEUKEMIC CELLS IN A RAT MODEL FOR HUMAN ACUTE MYELOCYTIC LEUKEMIA. I. VELOCITY SEDIMENTATION.

Hagenbeek A, Martens AC, Van Bekkum DW
Bone Marrow Transplant Unit, Center for the Health Sciences, Univ. California Los Angeles Sch. Medicine Los Angeles, CA, 90024
Leuk Res; 5(4/5):421-428 1981

The efficacy of the velocity sedimentation procedure was studied in a rat leukemia model (BNML: acute myelocytic leukemia in Brown Norway rats). Sedimentation rate profiles of spleen colony forming units (CFU-S) and leukemic CFU-S (LCFU-S) were determined. DNA histograms were prepared from leukemic cells sedimenting at three different rates in an attempt to correlate the sedimentation rate (and thus cell size) with the DNA content, which reflects a certain phase of the cell cycle (G0/G1, S, G2 + 1/2 M). The efficacy of the method was also evaluated by subjecting different mixtures of normal marrow cells and leukemic cells to separation and thereafter injecting the various fractions into normal recipient rats to determine whether or not they would die from leukemia. Normal and leukemia bone marrow cells showed two distinct overlapping peaks. The leukemic cells included up to 50% dead cells. The viable leukemic cells were almost exclusively found in the 'fast' peak of the leukemic profile. The ratio of dead and viable cells was 1:1. Viable and leukemic marrow cells showed peak sedimentation values of 2.5 and 7 mm/hr, respectively. Cells in different cell cycle phases sedimented at different rates. Based on absolute numbers of CFU-S and LCFU-S/sedimentation fraction, it was calculated that, below a sedimentation rate of 4.5 mm/hr, 70% of the CFU-S and 1% of the LCFU-S were recovered. The number of leukemic cells/injected fraction expressed as a percentage of the number of leukemic cells present in the original mixtures was maximally 0.8% and 0/7% for two sedimentation experiments. Thus, the minimal elimination factors were 120 and 150, respectively. The data suggested that if there is a contamination of one leukemic cell/2,000-10,000 normal bone marrow cells, ie per 14-70 hemopoietic stem cells, separation can be complete. (28 Refs)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

7. CELL KINETIC AND CYTOLOGICAL GRADING OF PROSTATIC CARCINOMA.

Helpap B
Pathologisches Institut der Universitat Bonn, Postfach 2120, D-5300 Bonn 1, W. Germany
Virchows Arch [Pathol Anat]; 393(2):205-214 1981

In 69 cases of prostatic carcinomas the 3H-thymidine labeling index was studied, and a cytological analysis was performed in addition to the histological classification. The following cytological variables were measured: nuclear size and shape, nuclear-cytoplasmic-ratio, nuclear chromasia, size and form of nucleoli. Only prostatic carcinomas with a labeling index of less than 0.4% showed mild nuclear anaplasia. These carcinomas were histologically classified as well differentiated adenocarcinomas. Prostatic carcinomas with a labeling index from 0.4% to 1.0% showed moderate nuclear anaplasia. These carcinomas were poorly differentiated adenocarcinomas. Carcinomas with labeling indices between 1.4 and 2.3% had moderate - marked nuclear anaplasia and exhibited a transition to undifferentiated carcinomas. Carcinomas with a labeling index higher than 2.3% were cribriform and undifferentiated carcinomas with marked nuclear anaplasia. The present studies have shown a correlation between both histological classification and cytological appearances with indicators of cell kinetics. (Author abstract) (29 Refs)

8. CYCLIC NUCLEOTIDES AND CELLULAR KINETICS IN NORMAL AND ABNORMAL HUMAN TROPHOBLASTIC TISSUE.

Masuko K, Tojo S
(c/o Tojo) Dept. Obstetrics and Gynecology, Kobe Univ. Sch. Medicine, 7 Kusunoki-cho, Ikuta-ku, Kobe (650), Japan
Arch Gynecol; 230(4):335-344 1981

Autoradiographic analysis of DNA synthesis was performed in normal trophoblastic cells and trophoblastic cells of hydatidiform moles and invasive moles. DNA synthesis alone was found to be an unreliable measure of trophoblastic cell activity, but duration of S phase (Ts) was a better indicator. Ts was 7 hr for normal villi and 10 hr for hydatidiform mole. Addition of cyclic AMP (cAMP) increased the duration of G1 phase in each tissue, while addition of cyclic guanosine monophosphate (cGMP) increased it. cAMP inhibited the cytotrophoblast from G1 phase to S phase, while cGMP promoted it. Intracellular cAMP concentration in normal cells was highest in early G1 phase. Apparently the maturative cell compartment was increased by cAMP and decreased by cGMP; the maturative cell compartment may be in G0 phase and thus intermediate between cytotrophoblast and syncytiotrophoblast. (16 Refs)

9. THE DURATION OF CELL CYCLES AND PROLIFERATIVE POOL OF THE HUMAN STRAINS OF GASTROINTESTINAL TRACT CANCER TRANSPLANTED IN NUDE MICE.

Revazova ES, Petrova AS
Center Oncology Res., USSR Acad. Medical Sciences, Moscow, USSR
Vopr Onkol; 27(8):46-49 1981

The duration of cell cycle and proliferative pool of the human strains of cancers of the stomach, liver and colon transplanted in nude mice were studied by the autoradiography method. The duration of cell cycles (26.4-16.9 hr) and proliferative pool (48.7-95.2%) were similar to those of the tumor strains in mice. (Author abstract) (9 Refs) (In RUS)

10. FLOW CYTOFLUOROMETRIC DNA ANALYSES ON METASTASES OF HUMAN MALIGNANT MELANOMA (MEETING ABSTRACT).

Hansson J, Tribukait B, Lewensohn R, Ringborg U
Radiumhemmet, Karolinska Hospital, Stockholm, Sweden
Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

Flow cytofluorometric analyses of DNA content was performed on cells from 38 sc and lymph node metastases from 32 patients with malignant melanoma. Thirty tumors yielded only one cell population, while 8 tumors contained two or more cell populations. Cells from 8 tumors had DNA patterns corresponding to diploid DNA values and the remaining 30 had aneuploid cell populations, mostly in the diploid to tetraploid region. No significant correlation between cellular DNA content and patient survival was observed. The proportion of S-phase cells was calculated from DNA histograms of cells obtained from 25 metastases in 21 patients. The number of S-phase cells varied from 3-34%. The number of S-phase cells was significantly higher in aneuploid as compared to diploid cell populations. Patients with a proportion of S-phase cells greater than or equal to 10% had a significantly shorter survival time as compared to patients with S-phase cells less than 10% (p less than 0.025). (no Refs)

11. DENSITY CENTRIFUGATION OF MURINE FIBROSARCOMA CELLS FOLLOWING IN SITU LABELLING WITH TRITIATED THYMIDINE.

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Cell Tissue Kinet; 14(6):589-600 1981

Murine fibrosarcoma (FSa) cells form at least five unique subpopulations after centrifugation in linear Renografin density gradients. Each of these subpopulations has been characterized with respect to selected kinetic parameters using pulse-labeling techniques and flow microfluorometry (FMF) analysis. Tumor-bearing mice were first injected ip with a pulse label of tritiated thymidine ([3H]TdR, 50 uCi). Following 15, 30, 60 min or 24 hr these animals were injected with cold thymidine. Animals were killed, their tumors removed and made into suspension, and separated by density gradient centrifugation. Each gradient was fractionated and the density, cell number, tritium activity, and labelling index (LI) per fraction were determined. These data were then compared to FMF data for selected cell density bands. The results indi cated a relatively higher uptake of [3H]TdR in the cells recovered at the lighter (1.06-1.12 g/cm3) as compared to the heavier (greater than 1.12 g/cm3) densities. Following a 30-min pulse, the LI's of light cells (less than 1.12 g/cm3) ranged from 25 to 30%, while the heavier cells (greater than 1.12 g/cm3) had LI's between 10 and 15%. The unseparated control cells had an LI of 19%. Comparable results were found at the other times tested. In contrast, the FMF profiles describing the DNA contents of the cells banding in the gradient showed no difference in proportion of S-phase cells among the separated subpopulations. This lack of correlation between the FMF determination of S-phase cells and labeling index for the denser cell populations implies that DNA content alone is not an effective measurement of the functional activity of cells in solid tumors. Finally, the relatively reduced uptake of [3H]TdR by these denser cells suggests that they may have resided at relatively large distances from the functional vasculature in the tumor. (Author abstract) (17 Refs)

12. THE CELL KINETICS OF EXPERIMENTAL MELANOMAS (MEETING ABSTRACT).

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Third European Workshop on Melanin Pigmentation, September 28-October 1, 1981, Prague, Czechoslovakia. Czechoslovak Medical Society 128 pp., 1981.

The cell kinetics of two murine melanomas of differing growth rates (B-16 and Harding-Passey) has been studied. As tumors grow the time of size doubling increased from 36 to 298 hr in melanoma B-16 and in Harding-Passey melanoma from 29 to 498 hr. The factors determining the retardation of the melanomas growth rate have been analyzed. The cell cycle duration changed from 12 to 18 hr between 13 and 24 days after B-16 melanoma and from 18 to 21 hr between 15 and 30 days after Harding-Passey melanoma. The proliferative pool was approx the same in these tumors and accounted for about 70% at early stages of the tumor development with subsequent reduction. The cell loss factor increased more essentially in Harding-Passey melanoma than in B-16 melanoma in the process of the tumor development. The contents of melanin and pigmented cells were extremely heterogeneous for both tumors. The mitotic index and labeling index after H3-thymidine were very similar for both melanomas. The low value of these indices observed in the most intensively pigmented tumors regions. But, in an hr after H3-thymidine labeled pigmented cells have been observed in these tumors. Evidently the proliferation and differentiation processes may take place simultaneously in these tumors. However one of these processes can be predominant in the different tumor region. (no Refs)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

13. CELL KINETIC CHARACTERISTICS IN DIFFERENT PARTS OF MULTICELLULAR SPHEROIDS OF HUMAN ORIGIN.

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Cell Tissue Kinet; 14(6):639-651 1981

The growth fraction, the cell cycle time, and the duration of the individual cell cycle phases were determined as a function of distance from the surface of multicellular spheroids of the human cell line NHIK 3025. The techniques employed were percentage of labeled mitoses and labelling index measurements after autoradiography and flow cytometric measurements of DNA histograms. To separate cell populations from the different parts of the spheroid, fractionated trypsinization was employed. The results were compared with corresponding values in NHIK 3025 cell populations grown as monolayer cultures. While practically all cells in exponentially growing monolayer populations are proliferating, the growth fraction was between 0.6 and 0.7 in the outer parts of the spheroid. The inner region was mainly occupied by a necrotic mass. The proliferating fraction of the recognizable cells in the inner region was slightly below 0.5. The mean cell cycle time of NHIK 3025 cells in monolayer culture is 18 hr. The mean cell cycle time of proliferating cells in the periphery of the spheroid was 30 hr, compared to 41 hr in the inner region (150 um from the spheroid surface). All phases of the cell cycle were prolonged compared

to populations of exponentially growing monolayer cells. Within each part of the spheroid the distribution of cell cycle times was considerably broadened compared with monolayer populations. (Author abstract) (31 Refs)

14. EFFECTS OF 17BETA-ESTRADIOL ON PROGESTERONE RECEPTORS AND THE UPTAKE OF THYMIDINE IN HUMAN BREAST CANCER CELL LINE CAMA-1.

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Cancer Res; 41(12):5004-5009 1981

Two sublines, CAMA-1R and CAMA-1N, were derived from the original CAMA-1 cells after continuous passages in our laboratory. 1R cells were supplemented in culture with estradiol and retained the properties of the original cell line, whereas 1N cells, not supplemented with estradiol, had a partial loss of estrogenic responsiveness. The doubling times for 1R and 1N cells were 2 and 2.4, respectively. These two sublines showed different effects on thymidine uptake after estradiol stimulation. Cells of 1R had a 2-fold greater thymidine incorporation than did the control without estradiol. In contrast, no difference of thymidine uptake was demonstrated in cells of 1N in the presence or absence of estradiol. Both cell lines contained cytoplasmic progesterone receptors with a Kd of 0.56 nM and a sedimentation coef ficient of 6 to 7S on a 5 to 20% sucrose gradient. The progesterone receptor level in 1N was about 8-fold higher than in 1R cells. Both sublines exhibited a dose-dependent increase in progesterone receptor levels in response to estradiol with the max stimulation (8-fold increase) reached by using 5 nmol of estradiol. The rate of increase for estradiol-induced progesterone receptor appears to be the same for both sublines; a linear increase was demonstrated between Days 3 and 7 following plating. Our results show that estrogen regulation of thymidine uptake and progesterone receptor induction may be mediated through two separate mechanisms. Thus, following a chronically deficient supply of estradiol to 1N cells, there is apparent loss of responsiveness to estradiol-induced thymidine uptake, but the ability of these cells to respond to estradiol induction of progesterone receptor was retained. (Author abstract) (30 Refs)

15. EXPRESSION OF TUMOR-ASSOCIATED ANTIGENS AND KINETIC PROFILE OF TWO IN VITRO HUMAN MELANOMA CELL LINES.

Badaracco G, Corsi A, Maisto A, Natali PG, Starace G, Zupi G
Istituto Regina Elena per lo Studio e la Cura dei Tumori, Rome, Italy
Cytometry; 2(2):63-69 1981

The growth characteristics and the antigenic profile of established human melanoma cell lines M10 and M14 are reported. While growth curves in culture, studied by flow cytometry, were fairly typical, there were some unusual features which were confirmed by their DNA distribution content. In the late stages of growth the cell DNA content resumes the initial distribution, suggestive of partial recovery of cell proliferating potentiai. Reactivity of three monoclonal antibodies (MoAb) to human melanoma associated antigens was assessed in normal and transformed melanocytes by indirect immunofluorescence (IIF). Staining of M10 and M14 lines with the three MoAb 225, 465 and Q5/13 showed that expression of melanoma-associated antigens as detected by IIF on the plasma membranes did not exhibit appreciable variations during the different growth phases studied during 4-13 days of culture. (9 Refs)

16. EFFECTS OF GROWTH STATE AND 3H LABELING LEVEL ON RNA TURNOVER IN WI-38 FIBROBLASTS AND HELA CELLS.

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Radiat Res; 88(2):333-342 1981

The basis for differential rates of RNA turnover in various cell types was investigated. It was found that the rate of turnover of RNA prelabeled with 3H-uridine in WI-38 cells varied with the amount of 3H-label incorporated, with the cell density of the cultures, and with the arrest of growth induced by senescence. The half-life of cells in cultures at higher density was 3.9 days, and about 7.5 days in culture diluted four fold until cells were nearly confluent, at which time the half-life decreased to 4.2 days. When the levels of 3H-uridine incorporation were too low to slow cell growth, the half-life of rRNA was consistently longer in cultures at lower density. The half-life of rRNA was the same in senescent cells diluted either 1-or 16-fold (3.0 days). The half-life of rRNA of established HeLa M and mouse L cells was 15 and 40 days, respectively. For cultures of WI-38 cells labelled with 0.01, 0.3 and 8.0 cpm/cells, the half-lives of RNA were 10.5, 8.0 and 5.0 days. Comparable levels of 3H incorporation had little effect on the rate of RNA turnover in several established cell lines, including SV-40 transformed WI-38 cells and HeLa cells. (19 Refs)

17. EFFECT OF TRANSFERRIN ON THE GROWTH OF A HUMAN RECTAL CANCER CELL LINE (MEETING ABSTRACT).

Morita A, Wong AD, Kim YS
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Gastroenterology; 80(5,part2):1235 1981

Transferrin was examined for its binding properties and effects on growth of a human rectal cancer cell line (HRT-18) in culture. Monolayers were cultured in multiwell plates in media containing 5% fetal bovine serum at 37 C with a 5% CO2 atmosphere and were subjected to binding studies using iodinated transferrin. Effects of transferrin on cell growth were assessed by culturing cells in serum-free synthetic medium in the presence and absence of purified human transferrin at varying concentrations for up to 14 days. Cells were able to grow satisfactorily in a serum-free synthetic medium in the absence of various hormones and growth factors. When included in a serum-free medium, transferrin stimulated cell growth. Doubling x of control cells was 3.5 days, while that of cells grown with 2ug/ml of transferrin was 1.8 days. Iodinated transferrin bound specifically to HRT-18 cells. Equilibrium of binding was attained within 20 min of incubation at 37 C and was shown to be saturable at a concentration of 40nM. Scatchard analysis of the binding data was best explained by a single linear line. The association constant (Ka) was found to be 1.3 x 108M-1 and the number of binding sites per cell was 1.8 x 10(5). In summary: 1) transferrin stimulates the growth of HRT-18 cells, and 2) transferrin specifically binds to HRT-18 cells. These data indicate that transferrin has a growth promoting effect on HRT-18 cells in culture and may affect the growth of some colonic maliignancies. (no Refs)

18. THE GROWTH OF PRIMARY HUMAN ADRENAL CONN'S ADENOMA CELLS IS HORMONE-DEPENDENT (MEETING ABSTRACT).

Armato U, Andreis PG, Mantero F
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In Vitro; 17(3):235 1981

Human adrenal Conn's adenomatous cells were cultured from aldosterone hypersecreting tumors according to a method used for the normal adrenal tissue. In such cultures the epithelial-like cells, exposed to Eagle's minimal essential medium added with 10% inactivated fetal bovine serum, were grouped in monolayered, homogenous colonies and were capable of spontaneous, though slow, proliferation. To identify the factors that affect the growth of these cells, 16-day-old cultures from 10 adenomata were treated for 5 days with daily doses of one of the following agents: ACTH, angiotensin II (AII), cyclic AMP, cyclic guanosine monophosphate (GMP), or with equimolar mixtures of the two hormones or cyclic nucleotides. When given singly, none of such agents could change the basal growth rate of the adenoma cells. In contrast, the mixture of cyclic AMP and GMP elicited a 3-to 4-fold increase in the fractions of cells entering S and M phases, thus doubling the number of adenoma cells within 5 days. Even the mixture of ACTH and AII promoted adenoma cell proliferation, being however only 60% as effective as the associated cyclic agents. The present results support the view that Conn's adenoma cell growth is hormonally controlled and may be mediated via both cyclic AMP and GMP; they also suggest that some other, as yet unidentified, growth factors(s), besides AII and ACTH, may be involved as well in the proliferative control of this histologically benign tumor. (1 Ref)

19. ANCHORAGE-INDEPENDENT GROWTH OF NORMAL CALF LENS EPITHELIAL CELLS AND EFFECT OF SV40 TRANSFORMATION ON THEIR GROWTH PROPERTIES.

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J Cell Physiol; 108(3):385-391 1981

The growth properties of normal calf lens epithelium and of Simian virus 40 transformants of these cells (SV LE.1 cells) were studied in relation to malignant change in epithelial cells. Growth of normal and SV LE.1 cells was obtained with a very low level of added mitogens. In low serum, the growth of SV LE.1 and normal lens cells appeared to be similar, although a higher cell density was reached by transformed cells at higher serum levels. In a medium containing 10% serum, SV LE.1 cells proliferated faster and achieved a higher density than did normal cells. Thus viral transformation decreased doubling time and increased final cell density when subject to strong mitogenic stimulus (high serum). Both normal and SV LE.1 cells formed mutlilayers when grown on plastic, the final cell density reached in 10% serum being 3.2 x 10(4) and 1.4 x 10(5)/square cm, respectively. It appeared that the constant number of attached cells in cultures of normal and SV LE.1 cells was maintained by cells detaching and being replaced by proliferating cells. There was considerable variation in the size of normal cells, but most of them were larger than the SV LE.1 cells. Of normal lens cells suspended in agar, 40-50% formed colonies that reached a size of 0.1-0.2 mm after 5 days in culture. The high cloning efficiency ruled out the possibility that colonies originated by aggregation. Growth from single cells was demonstrated. SV LE.1 cells formed colonies with a somewhat lower efficiency than lens cells, but the size of these colonies was larger. The results indicated that calf lens epithelial cells exhibit growth properties in vitro that have usually been associated with virally transformed fibroblasts. (23 Refs)

20. EFFECT OF 3,5,3'-TRIIODO-L-THYRONINE ON THE INCIDENCE AND GROWTH KINETICS OF SPONTANEOUS MAMMARY TUMORS IN C3H/HEN MICE.

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Cancer Res; 41(12):5015-5019 1981

The present study compares the incidence and growth kinetics of spontaneous mammary tumors in 3,5,3'-triiodo-L-thyronine (T3)-treated (0.7 ug/day, ip) C3H/HeN retired breeder mice with tumors occurring spontaneously in this strain (0.15 M NaCl, ip). T3 treatment markedly increased the rate of tumor incidence but had no effect on tumor growth rate as measured by tumor doubling time. A comparison of tumor labeling index and mitotic index between the two groups showed no difference. A histological comparison of the mammary glands in the two groups showed no significant difference in number of hyperplastic alveolar nodules. However, ductal-alveolar development was more pronounced in the 0.15 M NaCl-treated control group; consistent with this observation was the finding of lower levels of serum prolactin in the T3-treated group. Since mammary tumorigenesis was increased in T3-treated mice in spite of lower levels of serum prolactin, a well-known promoter of spontaneous mammary tumor in mice, a direct role for T3 in the process of tumor formation is suggested. (Author abstract) (45 Refs)

21. GROWTH RESPONSE TO INSULIN AND MSA IN MOUSE MELANOMA CELLS AND FIBROBLAST X MELANOMA HYBRIDS (MEETING ABSTRACT).

Coppock DL, Straus DS
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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Further studies have been performed with the PG19 mouse melanoma cells and one of the insulin-responsive hybrid clones to investigate the biochemical basis for the complementation for the insulin response observed in the hybrids. In hormone-supplemented serum-free medium, the hybrid cells but not the melanoma cells require insulin for optimal growth. Thus the growth response to insulin of the two cell types in serum-free medium is consistant with the growth response observed in confluent growth-arrested cultures. Like insulin, the insulin-like growth factor multiplication stimulating activity (MSA) stimula tes 3H-thymidine incorporation in the fibroblast x melanoma hybrid cells but not in the parental melanoma cells. The PG19 melanoma cells and the hybrid cells have approx the same number of high and low affinity insulin receptors, and both cell types also have high affinity MSA receptors. Interestingly, insulin strongly stimulates 3H-leucine incorporation in the hybrid cells over a broad concentration range, while in the melanoma cells it does not have a significant effect in most experiments and has a marginally significant effect in others. Two possible explanations for these results are that the melanoma cells have a postreceptor block in the growth response to insulin and MSA, or that processes controlled by insulin are never growth-limiting in these cells, whereas such processes can be made growth-limiting in the hybrids. One class of var-

iants appears to arrest more completely in medium with low serum than the parental hybrid cells, and to have a more stringent requirement for serum-derived growth factors for exit from G1. (1 Ref)

22. CHARACTERIZATION OF MURINE MELANOMA CELLS GROWN IN SERUM-CONTAINING AND SERUM AND HORMONE-FREE MEDIA (MEETING ABSTRACT).

Varga JM, Lambert DT, Airoldi L, Moellmann G, Bartholomew JC, Lerner AB
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Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

A subclone of the Cloudman S91 melanoma cells has been maintained in a serum- and hormone-free (EFO) medium for over one yr. These cells resemble those maintained in serum-containing medium having: a) an abundance of Stage II premelanosomes; b) the same karyotype as the parent strain; c) tumorigenicity in syngeneic mice. The cells grown in serum-containing media in that tyrosinase is not activated by either melanocyte stimulating hormone (MSH) or dibutyryl cyclic (c) AMP. Responsiveness to these agents can however, be recovered by maintaining the cells for a few passages in serum containing medium. The cells maintained in EFO also differ from those in serum in their growth and cell surface characteristics as determined by quantitative flow cytometry. We have found that cells grown in the presence of serum have a *'slow-down' in early S-phase.* When they are cultured in EFO medium they grow faster than in the presence of serum and the cells pass through S-phase without a slow-down. When the cells are cultured in EFO medium in the presence of dibutyryl cAMP, prostaglandin E1, or cytochalasin B, they show an early S-phase block which appears at the same relative position of DNA synthesis as the slow-down in the presence of serum. It is suggested that serum contains some factor(s) that inhibit DNA replication in melanoma cells. (no Refs)

23. GROWTH INHIBITION BY DEXAMETHASONE IN CLONAL VARIANTS OF HAMSTER MELANOMA CELLS: CHARACTERIZATION OF BIOLOGICAL RESPONSE AND ROLE OF MEDIUM COMPONENTS (MEETING ABSTRACT).

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Molecular Biology Division, University of Southern California, Los Angeles, CA
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

Dexamethasone (10 nM) inhibits the growth, alters the morphology and decreases the final cell density in RPMI 3460 Syrian hamster melanoma cells. We have isolated clonal variants of RPMI 3460, one of which (clone 6) exhibits the same three biological responses to dexamethasone (DM) the parental cell line. The other clone (clone 5), while exhibiting the decrease in final cell density, fails to exhibit the growth inhibition and morphological alterations. Since progesterone antagonizes the biological responses of clone 5 and clone 6 cells to DM, it appears that all the responses are mediated by glucocorticoid receptors. Experiments in which DM is added to or removed from logarithmically growing clone 6 cultures indicate that growth inhibition can be induced or reversed in less than 24 hr after DM addition or removal. Moreover, DM which is added during early or mid-logarithmic growth is able to evoke the decrease in final cell density and DM which is removed during early or mid-logarithmic growth has no effect on final cell density in clone 5 and clone 6 cultures. Interactions of DM with factors in fetal calf serum are unnecessary for DM action in logarithmically growing clone 6 cells. Moreover, these factors must not be involved in the different responses of clone 5 and clone 6 cells to DM. Studies with conditioned medium suggest that the different phenotypes of clone 5 compared to clone 6 cells are not due to differences in the ability of the two cell lines to alter the medium by producing extracellular resistance or sensitivity factors, either in the presence or absence of DM. (no Refs)

24. INHIBITION OF GROWTH OF HAMSTER PANCREATIC CANCER CELLS IN VITRO BY PGE2 AND 16,16-DIMETHYL PGE2 (MEETING ABSTRACT).

Mayschak DT, Flye MW
Department of Surgery, University of Texas Medical Branch, Galveston, TX, 77550
International Conference on Prostaglandins and Cancer, August 30-September 2, 1981, Washington, DC. Lombardi Cancer Center 75 pp., 1981.

Prostaglandins (PG) have been shown to both stimulate and inhibit various cancers in vitro and in vivo. This study determined the effect of prostaglandin E2 and the synthetic prostaglandin 16,16-dimethyl PGE2 on the hamster H2T pancreatic cancer cell line. Cells in exponential growth were treated for varying times with various doses of the prostaglandins, and the effect of treatment was gauged by studying doubling time, determining survival fraction, and characterizing perturbations in cell *cycle kinetics* by flow cytometry (FCM). Doubling time was increased by 50% with high doses of 16,16-dimethyl PGE2 and by 65% with equimolar doses of PGE2. Six-hr treatment with PGE2 yielded 20% kill with 50 ug/ml and 30% with 100 ug/ml, whereas a six-hr treatment with 100 ug/ml of 16,16-dimethyl PGE2 produced 80% kill. There is a time- and dose-dependent effect of the natural prostaglandin E2 and synthetic 16,16-dimethyl PGE2 in prolonging doubling time and decreasing survival fraction. These effects occur not only by a direct lethal influence of the prostaglandins, but also by partial blockade in the late S or early G2M phase of the cell cycle. (no Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

25. DNA SYNTHESIS AND CELL GENERATION PATTERN OF CHRONIC LYMPHATIC LEUKEMIA LYMPHOCYTES STIMULATED BY PHYTOHAEMAGGLUTININ.

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Cell Tissue Kinet; 14(6):633-638 1981

A detailed analysis of the cell recruitment and of the cell generation pattern of normal lymphocytes and chronic lymphatic leukemia (CLL) lymphocytes, simulated by phytohemagglutinin (PHA), was performed by the bromodeoxyuridine (BUdR) Hoechst technique. It was found that in normal cultures the majority of cells divide 2 or 3x, producing an early peak of DNA synthesis, while only a few cells grow exponentially and pass through many rounds of replication. On the

contrary, the majority of CLL responsive cells grow exponentially, producing a delayed peak of DNA synthesis, while cells which divide only 2 or 3x are scarce or absent. No difference in the minimal cell cycle length of the normal and the CLL exponentially growing population was found. In addition, a cell population recruited into cycle for the first time 5-6 days following PHA stimulation was observed in normal cultures but not in CLL cultures. (Author abstract) (24 Refs)

26. SIMULTANEOUS ANALYSIS OF DNA AND CELL SURFACE IMMUNOGLOBULIN IN HUMAN B-CELL LYMPHOMAS BY FLOW CYTOMETRY.

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Cancer Res; 41(12):4895-4899 1981

Cell suspensions prepared from human B-cell lymphomas were analyzed for cellular DNA and cell surface Ig (SIg) by flow cytometry. In addition to SIg-bearing neoplastic B-lymphocytes, these tumors contain nonneoplastic cells. Flow cytometry permitted selective analysis of DNA in subpopulations defined by the membrane antigen SIg and also permitted analysis of SIg of subpopulations defined by DNA content. Because measurements of DNA and SIg were made simultaneously on each cell, physical sepa ration of cells was not required. Using propidium iodide as a fluorescent DNA probe and fluorescein isothiocyanate-labeled antibodies to stain SIg, differences in cellular DNA between SIg-bearing neoplastic cells and nonneoplastic cells from the same tissues could be demonstrated. Additionally, this simultaneous correlated analysis allowed assessment of the cell cycle dependence of SIg expression. Mean fluorescein isothiocyanate (SIg) fluorescence was greater in S- than G1-phase cells, but the ratio of mean fluorescein isothiocyanate fluorescence of cells in S phase to that of cells in G1 phase varied for different tumors. (Author abstract) (22 Refs)

27. SPONTANEOUS RELEASE OF T CELL GROWTH FACTOR FROM A PRIMATE LYMPHOID CELL LINE AND ITS EFFECT ON THE CELL CYCLE (MEETING ABSTRACT).

Rabin H, Brown RL, Hopkins RF, Neubauer RH, Ruscetti F
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

In efforts to find an alternative to culture fluids from mitogen stimulated lymphocytes for production of T cell growth factor (TCGF), we tested culture fluids from five primate T cell lines for their ability to support growth and DNA synthesis of antigen or mitogen stimulated T cells. Only fluids from MLA 144 cells, a line established from a spontaneous lymphoma in a gibbon were positive. MLA 144 culture fluids (MTCGF) were comparable to TCGF from phytohemagglutinin (PHA) stimulated lymphocytes (PTCGF) in their support of growth and DNA synthesis of human and owl monkey T cells and colony formation in agar medium by human T cells stimulated with PHA. For cell cycle studies a partially TCGF-dependent owl monkey tumor T cell line, OMT-1, was used. In the absence of MTCGF for 48 hr, one population doubling occurred. By 96 hr without TCGF, no further population doubling took place but the cells remained viable as determined by trypan blue exclusion. In the presence of MTCGF the cells doubled two to three x within 96 hr with no decrease in cell viability. Cells kept in the absence of MTCGF incorporated 3H thymidine for 32 hr whereas those grown in the presence of MTCGF continued to incorporate 3H thymidine for 60 or more hr. The presence of MTCGF resulted in a two-fold increase in incorporation of 3H thymidine over the 60-hr period compared to controls. MTCGF appears to simulate proliferation of OMT-1 cells by overcoming delays within the G1 phase of the cell cycle. (no Refs)

28. G1-PHASE ARREST OF CULTURED HUMAN LEUKEMIC T-CELLS INDUCED BY DEOXYADENOSINE.

Fox RM, Kefford RF, Tripp EH, Taylor IW
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Cancer Res; 41(12):5141-5150 1981

Cultured human T-cell leukemia lymphocytes have enhanced sensitivity to growth inhibition by deoxyadenosine. We have used flow cytometry to investigate the mechanism of deoxyadenosine toxicity in cultured T-leukemic cells. Comparative studies on deoxyadenosine-resistant Epstein-Barr virus-transformed B-lymphocyte cell lines were also performed. After exposure of T-cells to low concentrations of deoxyadenosine (3 uM), in the presence of an adenosine deaminase inhibitor (erythro-9-[3-(2-hydroxynonyl)]adenosine), accumulation of cells of cells with a G1 DNA content was demonstrated. In contrast, B-cell lines showed a similar degree of growth inhibition after exposure to 200 to 400 mM deoxyadenosine but were blocked in S phase. The T-cell G1 block was associated with a rise in the deoxyadenosine triphosphate pool, and both these phenomena were prevented by the addition of deoxycytidine. The biochemical mechanisms of this G1 block induced by deoxyadenosine in T-cells is not understood. (Author abstract) (25 Refs)

29. PROLIFERATION AND MATURATION OF HAEMOPOIETIC CELLS IN PATIENTS WITH DIFFERENT FORMS OF HAEMOPOIETIC DYSPLASIA/ PRELEUKEMIA/IN AGAR AND LIQUID CULTURES AND DIFFUSION CHAMBERS (DC) (MEETING ABSTRACT).

Afanasiev BV, Elstner E, Schulze E, Podoltseva EI, Tiranova SA, Schutt M, Ihle R
1st Pavlov Institute of Medicine, Leningrad, USSR
Exp Hematol; 9(Suppl9):156 1981

Forty patients with different forms of hemopoietic dysplasia (HD) were investigated in double-layer agar culture by PIKE, ROBINSON and in liquid Marbrook system by GOLDE, CLINE. It was possible to characterize four types of growth pattern in bone marrow cell agar cultures. The bone marrow cells from 25% of the HD patients showed a hypoplastic growth pattern in agar, 20% a normal, 5% a hyperplastic and 50% a leukemic pattern. A significant correlation was observed between growth pattern and clinical course. The HD patients with normal and hyperplastic growth pattern had more benign course as compared to such with hypoplastic and leukemic type of growth. Progression to overt leukemia was more common in patients with a leukemic growth pattern. In agar cultures we observed a maturation defect in 6 of 10 patients. All of them exhibited a leukemic growth pattern. Three of 10 patients with normal and hyperplastic culture patterns showed a normal maturation. Six of 12 patients with HD showed a defective maturation in Marbrook cultures on day 7. The growth of hemopoietic cells in liquid cultures did not predict the risk of progression to overt leukemia in patients with HD. There was no clear-cut correlation between the number of colonies and clusters in agar cultures and the granulocytomonopoiesis in liquid cultures or in the DC. (no Refs)

30. DIFFERENCES IN THE REGULATION OF MURINE GRANULOCYTE AND MACROPHAGE GROWTH IN DIFFUSION CHAMBER CULTURES (MEETING ABSTRACT).

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Department of Medicine, Beth Israel Hospital, Boston, MA, 02215
Exp Hematol; 9(Suppl9):159 1981

As demonstrated under four sets of experimental conditions, murine macrophages do not respond to the same factors which influence granulocyte proliferation in diffusion chamber (DC) cultures: (1) When normal mouse bone marrow cells are cultured in DCs, a plateau in cell growth is observed after 7-10 days. During this plateau phase the same number of macrophages is observed regardless of the number of marrow cells placed in culture, whereas the plateau number of granulocytes varies in relationship to the number of marrow cells in the culture inoculum. (2) When DC cultures are established with marrow cells from donor mice which have been pretreated with 3 doses of cytosine arabinoside during the 14 hr before culture, macrophage growth is similar to that observed with cultures of normal marrow cells. In contrast, granulocyte growth in cultures derived from the marrows of drug-treated mice is enhanced by a factor of two. (3) When DC cultures of normal mouse marrow are implanted in host mice which have received 500 R whole body irradiation 24 hr earlier, growth of macrophages is unchanged whereas granulocyte growth is augmented, as compared to the findings with control cultures grown in unirradiated host mice. (4) When normal mouse bone marrow cells and murine acute myelogenous leukemic cells are cocultured in DCs, macrophage growth is unaffected whereas normal granulocyte growth is entirely abolished within a few days. In all four of these experimental situations granulocyte proliferation, but not macrophage growth, correlated well with the generation of colony forming units (CFU-C), as examined by serially harvesting DC cultures and assaying the cell contents in soft agar with L-cell conditioned medium as a source of colony stimulating activity. (no Refs)

31. MULTIPLE GROWTH PARAMETERS OF LYMPHOID CELL LINES TRANSPLANTED INTO NUDE MICE (MEETING ABSTRACT).

Kirchner HH, Gunzel M, Schaadt M, Fonatsch C, Diehl V
Abt. f. Haematologie/Onkologie, Medizinische Hochschule Hannover, Hannover, W. Germany
Exp Hematol; 9(Suppl9):88 1981

Tumorigenic potential of human hematopoetic cell lines in nude mice is not a marker of malignant cells only. To evaluate differences of the growth behavior of diploid, Epstein-Barr virus-transformed lymphoblastoid cell lines (LCL) considered to be non-neoplastic and malignant lymphoma lines (LL) three transplantation routes were examined: intracerebral (ic), sc/im inoculation of single cells suspensions and the sc transplantation of cells embedded in a fibrin clot. Additional to the tumor growth in the different modes of transplantation various parameters were analyzed: latency period, tumor progression, serial tran splantability, in vitro reculture success of nude mouse tumors. After intracerebral (ic) inoculation both types of lines were able to induce tumors with a rate of nearly 100%. Generally the LCL had a longer latency period and the rate of tumors which were macroscopically visible was only half of that compared to the lymphoma lines. Serial transplantation showed a constant latency period of tumor appearance with LL whereas with LCL there was an increasing interval between inoculation and tumor formation leading to a failure of tumor induction in a higher passage number. After sc/im transplantation of suspension cells only LL and old LCL with abnormal karyotypes were tumorigenic. The tumor growth curves showed an unlimited progression with similarity to the Gompertz function. When the cells were embedded in a fibrin clot before sc transplantation even diplloid LCL were able to induce tumors, but after initial exponential enlargement these nodules showed a tendency to regression and failed to grow in vitro after recultivation attempts as that stage. The in vitro recultivation of LCL induced tumors at the phase of logarithmic progression resulted in diploid cell lines. (no Refs)

32. ON THE MECHANISM OF BURST NUMBER ENHANCEMENT BY THE TUMOR PROMOTER TPA (MEETING ABSTRACT).

Brockbank KG
Department of Cell Biology and Genetics, Erasmus University, P.O. Box 1738, 3000 DR Rotterdam, The Netherlands
Exp Hematol; 9(Suppl9):132 1981

The addition of optimal concentrations of 12-O-tetradecanoyl-phorbol-13-acetate (TPA) or bone marrow conditioned medium as a source of burst-promoting activity (BPA) to the methylcellulose assay for rabbit erythroid burst-forming units (BFU-E) enhances burst number. The degree of burst enhancement by TPA and BPA is similar and when both TPA and BPA are added to the same culture no further enhancement of burst formation is observed. Thus, it is likely that the same population of erythroid precursors is responding to TPA and BPA. The mechanism by which TPA enhances burst formation is not known. A likely mechanism is that TPA mimics BPA. This hypothesis was examined by short-term incubation of bone marrow cells with either 30% bone marrow conditioned medium, 10-9M TPA, 3x10-9M TPA, 10-8M TPA or control medium. The % of BFU-e in S-phase of the cell cycle was then estimated after a second incubation for 2 hr in the presence and absence of 10mM hydroxyurea (HU). The bursts were counted after 10 days of culture. Incubation with BPA significantly enhanced in the HU kill after periods as short as 4 hr. TPA had very little effect on the % of BFU-e killed by HU. These results indicate that TPA does not mimic BPA. TPA enhancement of burst formation may indirectly stimulate BPA production by cells of the hemopoietic microenvironment or it may increase the responsiveness of BFU-e to the low levels of BPA present in the culture medium. (no Refs)

CELL CYCLE - SPECIFIC PHENOMENA

33. THE ALPHA-GLOBIN GENES ARE LOCATED IN A REGION OF EARLY-REPLICATING DNA IN FRIEND ERYTHROLEUKEMIA CELLS.

Furst A
Yeshiva University, New York, NY
Diss Abstr Int [B]; 42(3):876-B 1981

The time of replication in the S phase of regions of the mouse genome including the alpha-globin genes was determined in the Friend virus-transformed murine erythroleukemia cell line. Cells grown for short times in the presence of 5-bromodeoxyuridine (BUdR) were fractionated into synchronous populations by centrifugal elutriation. The DNA was cleaved by restriction endonucleases and fragments containing bromouracil (BU-DNA) were isolated in density gradients of cesium sulfate. BU-DNA fractions replicated during selected

intervals of the S phase were electrophoresed in agarose gels, transferred to diazobenzyloxymethyl paper, and hybridized to an alpha-globin probe. Reconstruction experiments using a cloned mouse Eco R1 fragment containing one of the alpha-globin genes demonstrated that the extent of hybridization provides an accurate measure of the concentrations of specific fragments in a DNA sample. The alpha-globin fragments were detected primarily in the BU-DNA replicated during early S. This result was confirmed in other experiments in which the methods of cell synchrony and of BU-DNA isolation were varied. The temporal replication of mouse satellite DNA sequences, already known from previous studies, was determined as an internal control for the cell synchrony. To show that the globin sequences were not lost from the cells in late S during isolation of the DNA, the alpha-globin fragments were quantitated in BU-DNA prepared from a mixture of cells in early and in late S. The results demonstrate that the alpha-globin gene regions are replicated during early S in these cells. (no Refs)

34. CELL CYCLE DEPENDENCY OF TUMOR PROMOTER ON MURINE ERYTHROLEUKEMIC CELLS (MEETING ABSTRACT).

Zucker RM
No affiliation given
Tenth International Symposium for Comparative Research on Leukemia and Related Diseases, August 31-September 4, 1981, Los Angeles, California. 187 pp., 1981.

The tumor promoter 12-O-tetradecanoyl-phorbol-13-acetate (TPA) affected the cell cycle of murine erythroleukemic cells (MELC). In logarithmically growing cells a transient G1 block lasting approx 6 hr developed after the addition of TPA. To investigate this cell cycle effect of TPA, cells were synchronized either by a double thymidine block or by centrifugal elutriation and were analyzed by flow cytometry and electronic nuclear vol. Using double thymidine blocked synchronized cells or elutriated separated fractions containing cells other than G1, a transient G1 block occurred as the cell entered early G1. The G1 elutriated cell population was blocked in the G1 period by TPA prior to cell cycle traverse . This transient block in G1 was not observed after the next cell cycle traverse. Addition of TPA to butyric acid (BA) or dimethylsulfoxide (DMSO) induced cells resulted in a transient G1 block in addition ot inhibition of differentiation. TPA was more inhibiting on DMSO induced cells than BA induced cells. (no Refs)

35. CELL CYCLE ARREST POINTS IN NONTUMORIGENIC AND TUMORIGENIC CELL LINES, DEPENDENCY ON GROWTH FACTORS (MEETING ABSTRACT).

Meiss HK, Marcus M
Department of Cell Biology, New York University Medical School, New York, NY
Growth of Cells in Hormonally Defined Media, September 1-4, 1981, Cold Spring Harbor, New York Cold Spring Harbor Laboratory 101 pp., 1981.

We found that the ability of the TM4 cells to traverse G1 depends upon epidermal growth factor (EGF) more than upon insulin (ins) or transferrin (trf) as illustrated by the fact that in cultures starved for 3 days for EGF, 86% of the cells are arrested specifically in late G1, while omission of ins or trf for 3 days resulted in the arrest in G1 of only 61 and 75% of the cells, respectively. When the cells are starved for isoleucine or serum, 61% of TM4 cells are arrested in late G1. However, in presence of ins and trf, 0.3% serum supports growth. Therefore, 0.3% serum seems to provide what EGF provides. The tumorigenic derivative of TM4, designated TM4-T which cannot grow in serum free (sf) medium was also analyzed for its growth requirements. We found that more than 90% of these cells are arrested in G1 when starved for either serum or isoleucine. However, whereas TM4 cells under similar starvation conditions are arrested in late G1, TM4 cells are arrested in early G1. Hittelman and Rao have shown that in confluent cultures contact inhibited cells are arrested in early G1 while transformed cells under similar conditions are arrested in late G1. We found that the tumorigenic rat Sertoli cell line TRST is less dependent upon the growth factors than is the nontumorigenic line TM4. In cultures starved for 3 days for either EGF or trf only 61% of the cells are arrested in late G1, while in cultures starved for 3 days for ins the distribution of cells is similar to that in the random cultures. However, in TRST cultures starved for serum or isoleucine the fraction of arrested cells in late G1 is similar to starved TM4 cells. (1 Ref)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

36. EFFECT OF 7-CON-O-METHYLNOGAROL ON DNA SYNTHESIS, SURVIVAL, AND CELL CYCLE PROGRESSION OF CHINESE HAMSTER OVARY CELLS.

Adams EG, Crampton SL, Bhuyan BK
Cancer Res., Upjohn Co., Kalamazoo, MI, 49001
Cancer Res; 41(12):4981-4987 1981

The effect of 7-con-O-methylnogarol (7-OMEN) on the survival of exponentially growing and plateau-phase Chinese hamster ovary cells was determined in a cloning assay. After 2 hr of exp osure, the 50% lethal dose for exponential and plateau-phase cells was 0.3 and 1.5 ug/ml, respectively. Drug doses for cell progression studies were based upon drug lethality; therefore, higher doses were used for plateau than for exponential populations. The effect of 7-OMEN on cell progression was studied by DNA flow cytometry under the following conditions: (a) during 24 hr of continuous exposure of exponentially growing cells; (b) during recovery of exponential cells after 2 or 7 hr of exposure; and (c) during recovery of plateau-phase cells after 2 hr of exposure. Exponential cells exposed continuously for 24 hr progressed normally from M to G1 phase and from G1 to S phase progression through S phase was slowed, and cells were ultimately blocked in G2 + M. Inhibition of S-phase progression was dose dependent, 0.2 ug/ml having only slight effect and 1.0 ug/ml accumulating a large fraction in S phase. Inhibition of S-phase progression correlated with DNA synthesis inhibition. Similar inhibitory effects were observed after pulsed (2-or 7-hr) exposure of exponential cells. 7-OMEN also blocked plateau-phase cells in G2 + M after 2 hr of exposure, but higher doses (3.0 ug/ml) were required. Simultaneous exposure of exponential cells to Colcemid (which blocks cells in metaphase) and 1.0 ug 7-OMEN per ml completely inhibited the expected increase in mitotic index, indicating that the G2 + M block observed by DNA flow cytometry was a block in G2 or prophase. (Author abstract) (19 Refs)

37. EFFECTS OF PULSE AND CONTINUOUS INTRAVENOUS INFUSION OF CIS-DIAMMINEDICHLOROPLATINUM ON L1210 LEUKEMIA IN VIVO.

Moran RE, Straus MJ
Div. Neoplastic Diseases, Dept. Medicine and Biochemistry, New York Medical Coll., Valhalla, NY, 10595
Cancer Res; 41(12):4993-4996 1981

The in vivo effects of cis-diamminedichloroplatinum on L1210 leukemia were determined using DNA content distribution analysis by flow microfluorometry and pulse [3H]thymidine labeling indices. Pulse and continuous infusion schedules were investigated. Pulse cis-diamminedichloroplatinum (2 and 6 mg/kg) resulted in progression delay of cells in S and G2 phases and at higher doses (greater than or equal to 12 mg/kg) in G1 as well. Equivalent total doses administered by continuous infusion over 24 to 72 hr delayed cells in G2 with little apparent affect on G1 or S progression. A max survival of 70% increased life span over controls was achieved with a 12-mg/kg pulse. Infusion doses at least 2-fold higher were required to achieve similar increases in survival. Cell cycle changes did not predict for therapeutic benefit, suggesting that, at suboptimal doses, cells were capable of repair. The therapeutic index for both modes of administration was narrow. (Author abstract) (17 Refs)

38. HYPERTHERMIC POTENTIATION OF DOXORUBICIN (ADRIAMYCIN) AND CYCLOPHOSPHAMIDE IN A TRANSPLANTABLE NEUROGENIC RAT CELL LINE (BT4) IN BD-IX RATS (MEETING ABSTRACT).

Dahl O
Department of Oncology, University of Bergen, 5016 Haukeland sykehus, Bergen, Norway
Strahlentherapie; 157(9):616 1981

The lethal effect of hyperthermia alone and the effect of combined hyperthermia and doxorubicin for the cell line in culture has been presented earlier. These results have been compared with recent experiments using the same cell line in BD-IX rats treated by immersion of the tumor-bearing feet in a water bath. The in vitro surviving fraction correlated very well in log-linear relation with the observed growth delay (difference in tumor doubling time in treated and control animals, normalized to the doubling time for control animals) after hyperthermia at 42-45 C. The synergistic effect of heat and doxorubicin found in culture could not be reproduced in vivo when 7 mg/kg doxorubicin was given iv 30 min before heating one hr at 44 C. At this temperature and dosage the combined effect was additive. The combined effect of hyperthermia (one hr at 44 C) and cyclophosphamide (200 mg/kg one hr before heating) had a striking synergistic effect in vivo. (2 Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

39. DIFFERENTIATED CELLS FROM BALB/C MICE DIFFER IN THEIR RADIOSENSITIVITY.

Rahmsdorf HJ, Ponta H, Bachle M, Mallick U, Weibezahn KF, Herrlich P
Kernforschungszentrum Karlsruhe, Institut fur Genetik und fur Toxikologie von Spaltstoffen, D-7500 Karlsruhe 1, W. Germany
Exp Cell Res; 136(1):111-117 1981

Various isolated cells of an inbred mouse strain (BALB/c) differed widely in their sensitivity to gamma irradiation: fibroblasts are 5 x more resistant than peripheral lymphocytes. Among lymphocytes, T cells are more resistant than B cells. Cell lines derived from the primary cells conserved their radiosensitivity. Cytofluorometric measurements show that the differential reaction of a cell to gamma irradiation can be detected already 2-3 hr after the irradiation event. Radiation-sensitive cells are delayed for a longer time in S phase and G2 phase of the cell cycle than radiation-resistant cells. No difference in the capacity of the cells to perform single-strand break repair, double-strand break repair or unscheduled DNA synthesis could yet be detected. (Author abstract) (24 Refs)

40. PARAMETERS OF A CELL POPULATION SYNCHRONIZED FOR RADIOSENSITIVITY STUDIES.

Bettega D, Fuhrman Conti AM, Rovida E, Scaioli E, Tallone Lombardi L
(c/o Tallone Lombardi) Istituto di Fisica dell'Universita, Via Celoria, 16, 20133 Milano, Italy
Radiol Med (Torino); 67(10):749-755 1981

Radiosensitivity studies were conducted during different phases of the cell cycle in synchronized cultures of human epithelial cells. Cells were grown in monolayers on veal serum with 15% Ea gle's medium and synchronized by the mitotic harvest method. The degree of synchronization was determined by different tests (growth curve, mitotic index, cell-size distribution) during the first duplication interval. Initial synchronization index was greater than 90%, after a time interval corresponding to the duplication time, it was 20-40%. Desynchronization velocity was approx 2%/hr. The radiosensitivity curve for cells exposed to 31 million electron volts, showed minimum resistance at the end of phase G1 and max resistance in S phase. The max/minimum sensitivity ratio for a dose of 1.75 Gy was 1.4. (11 Refs) (In ITA)

41. CYTOSINE ARABINOSIDE INDUCED RADIOPROTECTION OF INTESTINAL STEM CELLS (MEETING ABSTRACT).

Hanson WR, Boston DL
Department of Radiation Therapy, Rush-Presbyterian St. Luke's Medical Center, 1753 W. Congress Parkway, Chicago, IL, 60612
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

Pretreatment with the S phase specific cytotoxic agent cytosine arabinoside (Ara-C) protects the intestinal stem cells from gamma radiation injury by nearly tenfold. Studies were undertaken to test whether an altered cell age distribution could account for the duration and degree of protection and to measure the degree of protection from the high energy neutrons of the Fermi Lab Cancer Treatment Facility. Twelve hr after pretreatment with Ara-C, B6CF1/ANL mice were exposed to in-

creasing small doses of either 137Cs gamma or Fermi fast neutrons (fn), or selected split doses at intervals of 1, 2 and 3 hr between Fermi fn. The mice were sarcificed and the number of regenerating microcolonies per jejunal circumference in Ara-C treated and irradiated animals was compared to irradiated controls. Another group of mice was given Ara-C but in the 12 hr interval between Ara-C and irradiation, colcemid was given every 3 hr to continuously block and kill cells in mitosis. The results suggest that Ara-C given 12 hr prior to Fermi fn protects intestinal stem cells to nearly the same degree as it does for 137Cs gamma damage. Furthermore, the control split dose recovery ratio to Fermi fn at 1, 2 and 3 hr was 1.8 and was unchanged 12 hr after Ara-C. Colcemid reduced the crypt cell population to less than half the normal 250 cells per crypt; however, the cell survival curve was unaltered from the survival curve 12 hr after Ara-C. These results suggest that Ara-C recruits intestinal clonogenic stem cells, but inhibits their normal passage through DNA synthesis. These cells, responsible for intestinal mucosal regeneration, appear to be held in a radioresistant portion of the cell cycle for a period of about 10-16 hr after Ara-C. (1 Ref)

42. AN EXPLANATION FOR THE ABILITY OF CYTOTOXIC DRUG PRETREATMENT TO REDUCE BONE MAR ROW RELATED LETHALITY OF TOTAL BODY IRRADIATION (TBI) (MEETING ABSTRACT).

Millar JL, Stephens TC, Wist EA
Institute of Cancer Research, Sutton, Surrey, England
Conference on Chemical Modification: Radiation and Cytotoxic Drugs, September 17-20, 1981, Key Biscayne, Florida. Committee for Radiation Oncology Studies 139 pp., 1981.

Mice given 10 Gray (Gy) TBI died a hematological death 10 to 14 days after exposure. This lethality was avoided by pretreatment with a cytotoxic drug two or three days before irradiation. The best example of this was seen when 200 mg/kg cytosine arabinoside (ARA-C) was given two days before 10 Gy TBI when all the animals survived compared with no survivors in the group that received radiation alone. It was demonstrated that improved survival resulted from an earlier onset in the recovery of the pluripotent hemopoietic stem cells (CFU-S) in animals given ARA-C two days before irradiation. In animals given radiation alone there was a lag phase in the recovery of the CFU-S and drug pretreatment before irradiation abolished this delay. Our explanation of this phenomenon involves the widely held belief that the CFU-S are not a homogenous population of cells with regard to proliferative activity and self renewal capability. We propose that the cells that repopulate the CFU-S compartment after depletion by drug or radiation are a subpopulation of the CFU-S with higher self-renewal capability, lower proliferative activity and higher radiosensitivity than the overall population. This model predicts that radiation on its own will deplete the cells with greater self-renewal capacity disproportionately. In the normal animal the cells with high self-renewal capacity are thought to be out of cycle (or proliferating very slowly) and not depleted by cytotoxic drugs designed to kill actively proliferating cells. If treatment with cytotoxic drugs triggers these cells into cycle and they are in the relatively radioresistant S phase at the time of irradiation, more would survive and repopulation of the CFU-S compartment would begin without a delay. (1 Ref)

43. CYTOGENETIC EVALUATION OF THE EFFECT OF HYPOXIA ON ANIMALS.

Bobkova NN
Inst. Medico-Biological Problems, Moscow, USSR
Genetika; 17(8):1493-1499 1981

Cytogenetic analysis of mice exposed to hypoxia showed significant increase of the mitotic activity and the frequency of poly- and hyperdiploid cells in the bone marrow on day 3 after exposure. Hypoxia caused slight decrease of the frequency of chromosome aberrations. (26 Refs) (In RUS)

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KINETIC METHODS AND MODELS

1. ISOLATION OF QUIESCENT CELLS FROM MULTICELLULAR TUMOR SPHEROIDS USING CENTRIFUGAL ELUTRIATION.

Bauer KD, Keng PC, Sutherland RM
Dept. Radiation Biology and Biophysics. Univ. Rochester, Rochester, NY, 14642
Cancer Res; 42(1):72-78 1982

A quiescent (nonproliferating) subpopulation was identified by flow cytometric analysis using two-step acridine orange staining in the EMT6/Rochester, NY subline multicellular

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tumor spheroid, an in vitro culture system which provides a cellular microenvironment which mimics that of many in vivo tumors. To isolate a viable quiescent cell subpopulation, centrifugal elutriation which allows for ce ll separation mainly on the basis of size was used. This technique provided single cells of relatively homogeneous cell vol which varied over a wide range (approx 100 to 5,000 cu um). Though the relatively small cell vol fractions were the most enriched (82%) in quiescent cells, such cells were also observed in significant numbers (approx 20%) even in the largest cell fractions. The cell clonogenicity of the various elutriation fractions were also assessed and shown to be lowest (plating efficiency approx 20%) in the small spheroid cells but relatively constant in fractions containing intermediate and large cells (plating efficiency approx 50%). Continuous [3H]thymidine labeling indicated a slower rate of accumulation of labeled cells in the small spheroid cells, which may result from the transition of proliferating spheroid cells to the quiescent compartment during the course of labeling. These findings indicate the utility of centrifugal elutriation for quiescent cell characterization in in vitro tumor systems. (Author abstract) (32 Refs)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

2. A COMPARATIVE STUDY OF SOME GROWTH CHARACTERISTICS AND CELL-SURFACE PROPERTIES OF NEOPLASTIC CELLS.

Bischoff P, Robert F, Donner M
Unit Experimental Cancerology and Radiobiology (U.95), I.N.S.E.R.M., Plateau de Brabois, 54511 Vandoeuvre-les-Nancy Cedex, France
Br J Cancer; 44(4):545-552 1981

Tumor cells from a polyoma-induced ascitic tumor were fractionated on the basis of the electrical charge on the cell surface by free-flow electrophoresis. Several characteristics of tumor cells have been investigated: (1) differences in the proliferation and antigenicity within the tumor at any point in time; (2) variation in proliferative potential with the ageing of the tumor. In early ascitic tumors, electrophoretically fractionated cells exhibit very similar proliferative characteristics. However, most DNA synthesis was found in slow-moving cells. The behavior of older tumors was different. Proliferative potential and DNA synthesis were weaker and restricted to slow-moving cells, suggesting that fast-moving cells in older tumors were resting cells. An enrichment in Ig-bearing cells was also found in slow-moving cell fractions, supporting the hypothesis of variability in expression of tumor-specific antigens. The role of cell-surface properties and cell kinetics is discussed in relation to electrical surface charge, which might be involved in cell dissemination and metastasis. Thus, free-flow electrophoresis represents a satisfactory approach to isolate tumor cell subpopulations with characteristics such as high proliferative potential or increased expression of tumor antigens. (Author abstract) (24 Refs)

3. MOVEMENT OF LARGE INTESTINAL MUCOSA AND ROTATION OF LARGE INTESTINAL CANCER CELL S.

Hattori T
Pathologisches Institut der Universitat Bonn, 5300 Bonn, W. Germany
Nippon Rinsho; 39(5):36-41 1981

Cellular movement of normal large intestinal mucosa, dynamics of growth of adenomas in the large intestine, and the dynamics of proliferation of large intestinal carcinoma were discussed. 3H-TdR autoradiography showed that carcinoma cells have a longer generation time, thus effecting mitosis, than normal proliferating cells; this generation time was thought to be about 3-7 days for cancer cells compared to 24-30 hr for normal cells. Due to prolongation of cancer cell life, there are no extreme variations in the growth fraction, and cancer cells have incidental destruction. That is to say, this type of cell death is not due to maturation but rather to sudden death of the mitotic cell due to malignant change in the surrounding stroma. The time it takes for a cancer to double its vol is about 1-3 mo for human cancers in general and about 1 yr to several yr for cancers of the large intestine. (26 Refs) (In JPN)

4. CELL CYCLE AND PROLIFERATIVE POOL OF HUMAN TUMORS TRANSPLANTED INTO ATHYMIC MICE.

Revazova ES, Petrova AS
Cancer Res. Center, Moscow, USSR
Biull Eksp Biol Med; 91(9):335-337 1981

Cells of human melanoma, Ewing's sarcoma, kidney carcinoma, and Wilms' tumor were transplanted into athymic BALB/c mice, and, when tumors reached 1,000 cubic mm in size, the animals were inoculated with 3H-thymidine. Analysis of proliferative activity based on autoradiographic studies showed that parameters of the cell cycle of the xenografted tumors corresponded to those of the experimental neoplasms. The cell cycles of all of the transplanted tumors were significantly shorter than those of the original human neoplasms. (9 Refs) (In RUS)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

5. THE SRC GENE PRODUCT (PP60SRC) OF AVIAN SARCOMA VIRUS RAPIDLY INDUCES DNA SYNTHESIS AND PROLIFERATION OF CALCIUM-DEPRIVED RAT CELLS.

Durkin JP, Boynton AL, Whitfield JF
Animal and Cell Physiology Group, Natl. Res. Council Canada, Ottawa, Ontario K1A OR6, Canada
Biochem Biophys Res Commun; 103(1):233-239 1981

Calcium-deprived tsLA23-NRK cells are reported to be blocked near the G1/S boundary of the cell cycle at 40 C, a temperature non-permissive for neoplastic transformation. Such arrested cells rapidly initiated DNA synthesis and resumed proliferating in calcium-deficient medium when the temperature was lowered to 36 C, a level permissive for the production of active pp60src and neoplastic transformation. In contrast, previous studies had shown that calcium-deprived wtB77-NRK cells grew rapidly and continuously at either 40 C or 36 C, while uninfected NRK cells were unable to proliferate at either temperature in calcium-deficient medium. The product of the src transforming gene of avian sarcoma virus may thus act near the G1/S border to rapidly bypass or directly stimulate a normally calcium-dependent process needed for the initiation of DNA synthesis. pp60src thus allows neoplastic, avian sarcoma virus-infected NRK cells to proliferate in calcium-deficient medium which does not support the proliferation of non-neoplastic counterparts. This work supports the suggestion that changes in protein kinase activities are responsible for the

ability of a wide variety of transformed avian, bovine, rodent and human cells to proliferate in calcium-deficient medium. (21 Refs)

6. EFFECTS OF INSULIN ON CELLULAR GROWTH AND PROLIFERATION.

Straus DS
Biomedical Sciences Div., Univ. California, Riverside, CA, 92521
Life Sci; 29(21):2131-2139 1981

Insulin stimulates the growth and proliferation of a variety of cells in culture. The growth-stimulatory effects of insulin are observed in G0/G1 arrested cells limited for serum growth factors or essential nutrients, and in cells growing in hormone-supplemented serum-free media. Some, but not all, of the effects of insulin on growth require superphysiological concentrations of insulin. The action of insulin on growth is synergistic with the action of other hormones and growth factors, including FGF, PDGF, PGF2alpha, and vasopressin. This observation, as well as other observations regarding the temporal sequence of action of growth factors, suggests that different growth factors act on different intracellular biochemical events. Several hypotheses have been proposed to explain the effect of insulin on cellular proliferation, including regulation of essential metabolic processes and interaction of insulin with receptors for insulin-like growth factors. Evidence supporting these various hypotheses is reviewed. In addition to the growth-stimulatory effect of insulin observed in cell culture, a number of clinical examples suggest that insulin is an important growth-regulating hormone during fetal development. (Author abstract) (87 Refs)

7. EFFECT OF SODIUM BUTYRATE ON THE HEPATOMA CELL CYCLE: POSSIBLE USE FOR CELL SYNCHRONIZATION.

Van Wijk R, Tichonicky L, Kruh J
Dept. Molecular Cell Biology, State Univ., Padualaan 8, 3584 CH Utrecht, The Netherlands
In Vitro; 17(10):859-862 1981

Exposure of HTC cells to sodium butyrate caused inhibition of growth. The site of growth inhibition was studied by time-lapse cinematography and [3H]thymidine incorporation studies. Evidence is presented that sodium butyrate affected the cell cycle at a specific point immediately after mitosis. Inasmuch as it does not modify the interphase duration after its removal, butyrate may be used for HTC synchronization. (Author abstract) (25 Refs)

8. CELL CYCLE ACTIVATION AND OUABAIN-SENSITIVE ION MOVEMENTS OF 3T3 AND C3HT1/2 FIB ROBLASTS.

Wenner CE, Cheney JC, Tomei LD
Dept. Experimental Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Supramol Struct Cell Biochem; 15(2):161-168 1981

The effects of phorbol esters and prostaglandin F2alpha (PGF2a) on cultures of 3T3-4 or C3H-10T1/2 mouse fibroblasts were studied to determine the relationship between activity of the Na+/K+ pump and cell proliferation. Uptake of 86Rb+ by 3T3-4 cells in the presence or absence of 10(-3) M ouabain after treatment with 12-O-tetradecanoyl-phorbol-13-acetate (TPA), 10% fetal calf serum (FCS), or PGF2a. Serum produced the greatest stimulation of 86Rb+ uptake, followed by 10(-7) M TPA. PGF2a stimulation was at an intermediate level. Both TPA and PGF2a stimulation were largely ouabain-sensitive. In postconfluent cultures the greatest stimulation of [3H]-thymidine (TdR) incorporation was produced by 10(-7) M TPA. PGF2a produced a smaller significant stimulation, which was not dose-dependent. In C3H-10T1/2 cells optimal 86Rb+ uptake was produced by 10(-8)-10(-6) M TPA. Both PGF2a and the inactive promoter 4-O-methyl-tetradecanoyl-phorbol-acetate produce small significant stimulation at a concentration of 10(-6) M. Stimulation in all three cases was 82-91% ouabain-sensitive. TdR uptake in C3H-10T1/2 cells was stimulated by TPA, but not by PGF2a. Results suggest a correlation between Na+/K+ pump activation and S-phase entry after TPA stimulation, but not after PGF2a stimulation. (18 Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

9. KINETIC PARAMETERS OF PROLIFERATING GRANULOCYTES IN PATIENTS WITH CHRONIC MYELOID LEUKEMIA.

Petukhov VI, Bondare DK, Baravika IIa, Velik LV
Dept. Leukozoology, Central Res. Lab., Medical Inst., Riga, USSR
Ter Arkh; 53(9):39-45 1981

Kinetic parameters of proliferating blood and bone marrow granulocytes were estimated in 10 patients (4 men, 6 women; 25-68 yr old) who had chronic myeloid leukemia (CML). Analysis of the growth fraction (GF), overall labeling index (q1), specific labeling index (q2), generation time (Tg), and rate of proliferation (Kb) showed a significant decrease in GF for all types of proliferating granulocytes. Myeloblasts were characterized by a decrease in GF, with simultaneous decrease in q1, while the values for q2, Tg, and Kb did not differ from those in healthy controls. (30 Refs) (In RUS)

CELL CYCLE - SPECIFIC PHENOMENA

10. THE IMPORTANCE OF DNA DAMAGE AND REPAIR IN THE CELL CYCLE SENSITIVITY OF CHO CELLS TO NITROGEN MUSTARD.

Clarkson JM, Mitchell DL
Science Park-Res. Div., Univ. Texas System Cancer Center, P.O. Box 389, Smithville, TX, 78957
Radiat Res; 88(3):587-596 1981

A large cell cycle effect was demonstrated for the survival of Chinese hamster ovary cells treated with nitrogen mustard; there was a 50-fold difference in survival between the most sensitive (G1) and the most resistant (G2) cell stages. This effect does not appear to result from different levels of DNA damage or repair at different cell stages. The role of DNA damage and its repair in cell lethality is discussed. (22 Refs)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

11. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF SANGIVAMYCIN IN HUMAN COLON CARCINOMA CELLS IN CULTURE.

Glazer RI, Hartman KD
NCI, Building 37, Rom 6D28, Bethesda, MD
Mol Pharmacol; 20(3):657-661 1981

The cytokinetic and biochemical effects of sangivamycin (SG) on human colon carcinoma in tissue were studied. Log phase and early plateau phase cells were exposed for 2, 24, and 48 hr to SG and cell viability was determined by soft agar cloning. Brief (2 hr) drug exposure of either log- or plateau-phase cells was not cytotoxic. Prolonging drug exposure to 24 or 48 hr dramatically increased cell lethality; 1 x 10(-6) M SG reduced cell viability of log phase cells by 83% and 97% after 24 and 48 hr of drug exposure, respectively, while cell viability was reduced in plateau-phase cells by 20% and 75%, respectively. Increasing the SG concentration to 1 x 10(-5) M increased cytoxicity only in plateau-phase cells. DNA synthesis was not significantly affected after 2 hr of drug exposure, but precipitously decreased following prolonged incubation with SG for 24 or 48 hr. In contrast, total RNA synthesis was initially inhibited up to 40% after 2 hr of exposure to 1 x 10(-5) SG, but was not reduced much further after longer intervals of drug treatment. RNA synthesis was not significantly inhibited in plateau-phase cells after 48 hr of drug exposure. In contrast, inhibition of non-poly(A)RNA and poly(A)RNA occurred to a degree comparable to that of total RNA in log-phase cells. The time and concentration dependence of SG incorporation into DNA and RNA correlated qualitatively with the effect of SG on cell viability. The incorporation of 3H-SG into poly(A)RNA correlated with the reduction in cell viability observed in log- and plateau-phase cells under comparable conditions. Results indicated that SG produces significant cell lethality to a human colon carcinoma which is generaly refractory to antitumor agents. (15 Refs)

12. CYTOKINETIC AND BIOCHEMICAL EFFECTS OF 5-IMINODAUNORUBICIN IN HUMAN COLON CARCINOMA IN CULTURE.

Glazer RI, Hartman KD, Richardson CL
NCI, Building 37, Room 6D28, Bethesda, MD, 20205
Cancer Res; 42(1):117-121 1982

The semisynthetic anthracycline, 5-iminodaunorubicin (IM), was investigated to see whether modification of the benzoquinone moiety to produce a drug with low free radical potential would alter the cytotoxic and biochemical characteristics of this drug in comparison to Adriamycin (ADR), an agent with high free radical potential. Cell viability was measured in human colon carcinoma (HT-29) cells by soft-agar cloning. Upon exposure of either log-phase or early plateau-phase cells for 2 hr to IM or ADR, a threshold exponential cell lethality curve was obtained. Prolonging drug exposure to 24 hr produced an exponential decline in cell survival and a marked reduction in viability of both log-phase and early plateau-phase cells. Inhibition of DNA synthesis in log-phase cells after 2 and 24 hr of exposure to IM and ADR paralleled the increased cell lethality produced by the drugs. In contrast, total RNA synthesis was not inhibited by IM, whereas ADR impaired both RNA and DNA synthesis. Nuclear rRNA synthesis was not significantly inhibited following 24 hr of exposure to 10(-7) M ADR or IM but was inhibited by 85 and 35% at 10(-6) M ADR or IM, respectively. The affinity of IM and ADR for HT-29 DNA was measured in vitro by displacement of acridine orange binding and was found to be similar for both analogs. These studies suggest that the cytotoxicity of IM and ADR results from the interactions of these drugs with DNA. (Author abstract) (20 Refs)

13. LETHAL ACTIVITY AND KINETIC RESPONSE OF CULTURED HUMAN CELLS TO 4'-(9-ACRIDINYLAMINO)METHANESULFON-M-ANISIDINE.

Drewinko B, Yang LY, Barlogie B
Dept. Lab. Medicine, Univ. Texas System Cancer Center, M.D. Anderson Hosp. and Tumor Inst., Houston, TX, 77030
Cancer Res; 42(1):107-111 1982

Cytotoxic and cytokinetic effects of 4'-(9-acridinylamino)methanesulfon-m-anisidine (m-AMSA) were studied on a cultured human colon carcinoma and on a human lymphoma (T1) cell line. Proliferating cells were more susceptible (10-fold) to the cytotoxic effect of m-AMSA than were nonproliferating cells. The agent had minimal effects on DNA synthesis. A comparable exposure doses on m-AMSA, the degree of lethal cell damage exceeded inhibition of DNA synthesis by four-fold. Cells synchronized in different stages of the cell cycle were equally sensitive to the cytotoxic effects of the drug, although the major cytokinetic effect was a block in G2. A greater killing effect was obtained by fractionated delivery than by a comparable dose delivered at once. These results suggest that superior antitumor results may be achieved by adequately spaced low doses of m-AMSA in the treatment of sensitive human tumors. (Author abstract) (34 Refs)

14. CELL POPULATION KINETICS IN HAIRLESS MOUSE EPIDERMIS FOLLOWING A SINGLE TOPICAL APPLICATIONS OF 12-O-TETRADECANOYLPHORBOL-13-ACETATE I.

Astrup EG, Iversen OH
Inst. Pathology, Univ. Oslo Rikshospitalet, Oslo 1, Norway
Carcinogenesis; 2(10):999-1006 1981

Cell population kinetics of hairless-mouse (Oslo strain) epidermis following a single, topical application of 17 nanomoles of 12-O-tetradecanoylphorbol-13-acetate (TPA) were investigated by flow cytometry and by measuring thymidine incorporation into DNA, mitotic index, and colcemid-arrested metaphase rates. The early epidermal cell kinetic reaction to TPA was divided into two periods: period 1 (0-12 hr), characterized mainly by a block in cell proliferation, and period 2 (12-96 hr), characterized mainly by rapid proliferation leading to hyperplasia. Thus, TPA treatment leads to an immediate block of cells in S-phase and mitosis, thereby triggering the cells to proceed, partly synchronized, through several cycles of cell division. The fact that hyperplastic epidermis is composed of a higher proportion of young, immature cells, which are functionally and morphologically different from mature cells, may account for some biochemical changes occurring after TPA application. (48 Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

15. THE FIRST TWO MITOTIC CYCLES IN HUMAN LYMPHOCYTES IRRADIATED AT DIFFERENT STAGES.

Poriadkova NA
Res. Inst. Medical Radiology, Obninsk, USSR
Radiobiologiia; 21(5):712-715 1981

The effect of irradiation at different stages of cell division on the kinetics of the mitotic cycle was studied in human peripheral blood lymphocytes. The lymphocytes were irradiated with gamma rays (200 rads) during the G0, late G1, S, and G2 phases; duration of the first mitosis after irradiation was assessed by sister chromatid differential staining technique. Irradiation at G0 did not affect the duration of the first mitosis, irradiation at G1 and S increased the duration 4 hr, and irradiation at G2 increased the duration by 8 hr. (9 Refs) (In RUS)

16. MODIFICATION OF THE INTESTINAL POSTIRRADIATION PROLIFERATIVE RESPONSE BY INTRAABDOMINAL H-4-II-E2 TUMORS.

Evans MJ, Kovacs CJ, Schenken LL, Burholt DR
Dept. Radiology, Div. Radiation Oncology, Bowen Gray Sch. Medicine, Winston-Salem, NC, 27103
Radiat Res; 88(3):552-564 1981

Changes in the steady-state kinetics of the male ACI rat intestinal epithelium accompanying intraabdominal growth of the H-4-II-E2 hepatoma cell line and subsequent alterations of the response of the host jejunum to abdominal irradiation are described. Ip injection of culture E2 cells resulted in growth of numerous nodules concentrated in areas of high vascularization. The mean tumor-mass doubling time was 15 hr between days 6 and 11, and 57 hr between days 11 and 14. The proliferative activity of the tumors decreased as a function of total tumor burden rather than individual nodule size. Progressive growth of the ia H-4-II-E2 tumor resulted in a depression of proliferative activity in both jejunal and colonic tissue. The depression of intestinal proliferation in tumor-bearing animals estimated by 3H-thymidine incorporation reflected cytokinetic changes occurring within jejunal crypts. The rate of DNA synthesis remained constant during the course of initial cytokinetic changes but was decreased between days 12 and 16 of tumor growth. De pression of crypt cellularity was accompanied by a reduction in the number of mitotic cells in the jejunal crypt. Marked alteration in crypt steady-state kinetics and reduced cell production accompanying tumor progression resulted in a reduced migration rate of cells from the crypt through the villus. Increasing tumor mass at the time of irradiation did not alter the time course of response and recovery kinetics of the jejunum to radiation. The magnitude of the peak of radiation-induced compensatory response was progressively limited with tumor potential. (26 Refs)

17. CELL-STAGE-SPECIFIC ENHANCEMENT BY CAFFEINE OF THE FREQUENCY OF CHROMATID ABERRATIONS INDUCED BY X-RAYS IN NEURAL GANGLIA OF DROSOPHILA MELANOGASTER.

De Marco A, Polani S
Centro di Genetica Evoluzionistica, C. N. R. presso Istituto di Genetica, Universita di Roma, Rome, Italy
Mutat Res; 84(1):91-99 1981

The effect of caffeine on chromatid aberrations induced by x-rays in neural ganglia of Drosophila melanogaster was studied. Ganglia were removed from third-instar larvae and treated with colchicine (10(-3) M) to accumulate cells in mitosis. They were then exposed to caffeine (10(-2) M), x-rays (500 R), or both. Caffeine alone produced high rates of chromatid aberrations only when added to cells late in G2 phase or during mitotic prophase. Although caffeine alone did not induce aberrations during S-phase, middle G-phase, or C-mitosis, it did enhance the damage produced by x-rays. This enhancement was similar in all three phases. During S- and G2-phases damage consisted primarily of isochromatid deletions and chromatid exchanges. Treatment during C-mitosis produced all types of chromatid damage. Enhancement of X-ray-induced damage may be due to inhibition of DNA repair mechanisms by caffeine. (25 Refs)

OTHER RELATED STUDIES

18. METHYL METHANE-SULPHONATE (MMS) INDUCED SCES ARE REDUCED BY THE BRDU USED TO VISUALISE THEM.

Ockey CH
Paterson Lab., Christie Hosp., Holt Radium Inst., Withington, Manchester M 209 BX, England
Chromosoma; 84(2):243-256 1981

SCE induction in synchronized CHO cells treated with methyl methane sulfonate (MMS) in G1 was studied over successive pairs of cell cycles by introducing bromodeoxyuridine (BrdU) at consecutive G1 stages. When individual cell cycle SCE values were calculated from the data, anomalous results were obtained with ratios of 1.0:1.8:2.1 for the first three cycles but a negative value for the fourth cycle. Further studies using different BrdU concentrations showed that MMS induced SCEs were reduced by values exceeding 50% in DNA containing high levels of incorporated BrdU. This reduction was dose dependent and accounted for the anomalous results obtained over successive cycles. Lesions leading to chromatid exchanges were also reduced by the same mechanism. SCEs induced by UV irradiation were also decreased but th ose induced by the cross-linking agent nitrogen mustard (HN2) remained unaffected. The results indicate that not only are SCE lesions induced by MMS, UV or HN2 expressed independently of the 'spontaneous' SCEs induced by BrdU but that SCE lesions are multiple in nature. Mechanisms by which SCE lesions could be repaired in BrdU containing DNA are discussed. SCE lesions in MMS treated cells arrested in G1 with arginine deprived medium (ADM) are repaired without the presence of BrdU in the DNA. An opposite effect is seen however in the control cells, where SCEs are increased with time spent in ADM arrest. These interactions between the effects of MMS, BrdU and ADM arrest are discussed. (Author abstract) (14 Refs)

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KINETIC METHODS AND MODELS

1. PROLIFERATION KINETICS OF PERTURBED CELL POPULATIONS DETERMINED BY THE BROMODEOXYURIDINE-33258 TECHNIQUE: RADIOTOXIC EFFECTS OF INCORPORATED [3H]THYMIDINE.

Beck HP
Institut fur Biophysik und Strahlenbiologie, Universitat Hamburg, Martinistrasse 52, D-2000 Hamburg 20, W. Germany
Cytometry; 2(3):170-174 1981

Monolayer cultures of L-929 cells grown at 37 C were flash labeled for 30 min with 3H-thymidine (0.3 uCi/ml; 40Ci/milliM). Bromodeoxyuridine was added at intervals after labeling to obtain a final concentration of 3.30 ug/ml. Cells were stained with 10 ug/ml 33258 Hoechst, and flow cytometric measurements undertaken using a Phywe ICP 22 detector. Analysis of resulting histograms permitted determination of the growth curve, the efflux and influx for the G2 + M compartment, and the transit characteristics of cell cohorts through the G2 + M phase. Heavy perturbation of the proliferation kinetics of the labeled cells was observed. (19 Refs)

2. FLOW CYTOMETRIC ANALYSIS OF THE RESPONSE OF THE R3327-G RAT PROSTATIC ADENOCARCINOMA TO ENDOCRINE MANIPULATION.

Pollack A, Bagwell CB, Block NL, Irvin GL, Claflin AJ, Stover BJ
Res. Service 151, Veterans Admin. Medical Center, 1201 NW 16 St., Miami, FL, 33125
J Surg Oncol; 18(4):389-398 1981

The technique of flow cytometric DNA histogram analysis (FCM) shows there to be two distinct cell populations (diploid vs aneuploid) in the poorly differentiated R3327-G rat prostatic adenocarcinoma. The following study compares tumor wt measurements with several FCM computer-based methods designed to determine rapidly the proliferative status of tumors. Hypophysectomy, bilateral adrenalectomy, orchiectomy, sham operations, or diethylstilbestrol treatments were initiated when the tumors were palpable (day 21) and continued until the tumors were excised (day 52). Hypophysectomy, orchiectomy, adrenalectomy, and diethylstilbestrol treatments all resulted in significant inhibition by tumor wt. Quantitation of the percentage of mid-S phase aneuploid cells by summation gave the best correlation with tumor wt. Tumors grown in hypophysectomized, orchiectomized, adrenalectomized, or diethylstilbestrol-treated animals showed a significant reduction in the proportion of mid-S phase cells as compared with controls. The calculation of the percentage of all aneuploid cells was significantly reduced in hypophysectomy, orchiectomy, and diethylstilbestrol-treated animals. However, tumors grown in adrenalectomized animals were not significantly different from controls by this method. Adrenalectomy was found to be the least effective form of therapy, and this was reflected in all of the parameters measured. These data show that FCM analysis may be useful in the quantitation of prostatic carcinoma response to therapy. (Author abstract) (34 Refs)

3. FLOW CYTOMETRIC MEASUREMENT OF NUCLEAR DNA CONTENT VARIATIONS AS A POTENTIAL IN VIVO MUTAGENICITY TEST.

Otto FJ, Oldiges H, Gohde W, Jain VK
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Cytometry; 2(3):189-191 1981

Bone marrow samples from male NMRI mice administered cyclophosphamide (ip, 0.56-0.7 ml of 0.075-0.6% soln in physiological saline) were assayed for cellular DNA content. Staining was accomplished by addition of 9 ml disodium hydrogen phosphate containing 5 uM 4,6-diamidino-2-phenylindole, and fluorescence was measured by pulse cytophotometer. The coefficient of variation in the G1 peak of flow histog rams increased during the first few days (especially 2-4 days) after injection. Both the magnitude and duration of the effect were dose-dependent through a range of 0-120 mg/kg. Reproducibility of results was high. (6 Refs)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

4. HUMAN MALIGNANT MELANOMA HETEROTRANSPLANTED TO NUDE MICE.

Trope C, Johnsson JE, Alm P, Landberg T, Olsson H, Wennerberg J
Dept. Oncology., Univ. Hosp. of Lund, Lund, Sweden
Neoplasma; 28(5):585-591 1981

Five different human malignant melanomas were heterotransplanted subcutaneously to nude mice. When small tissue pieces were used three out of five tumors grew. Subcutaneous injections of suspended tumor cells were also made, but all failed to take. Metastatic or infiltrative growth was never seen in the mice observed for up to 2.5 months. The successful grafts largely retained the original morphological features. The three successfully transplanted tumors could all be serially transfered with 100% tumor take. In one case passage time was reduced from 40 days to 15 days. As measured with 3H-thymidine incorporation the proliferation rate increased during the passages. These changes might be due to a selection of more rapidly growing tumor cells in the nudes. (Author abstract) (16 Refs)

5. DNA MEASUREMENTS BY SINGLE NUCLEI FLOW CYTOMETRY IN HUMAN ACTINIC SKIN LESIONS.

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Dept. Dermatology, Hvidovre Hosp., Kettegards alle 30, 2650 Hvidovre, Denmark
J Invest Dermatol; 77(6):431-433 1981

A basal cell carcinoma, a Bowenoid carcinoma and clinically normal nonexposed skin from a 76-yr-old male with numerous epidermal tumors on sun-damaged skin were investigated by DNA flow cytometry and the results were compared with data obtained from normal skin of a control group. From each type of skin lesion three different biopsies were examined. Each of the DNA frequency distribution histograms showed bimodal configuration revealing no more than one DNA stem line, which was diploid in the unaffected skin and the Bowen carcinoma and hyperdiploid in the basal cell carcinoma. The three different types of skin could be clearly separated by means of at least one of three parameters: S-fraction, G2 + M fraction

or S/G2 + M index. The S/G2 + M index came out as the most sensitive discriminator for the tumors. The S-fraction level was higher in the clinically normal skin of the investigated male than in the control group and further high in the tumors. (Author abstract) (15 Refs)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

6. CELL CYCLE-SPECIFIC GLUCOCORTICOID GROWTH REGULATION OF A HUMAN CELL LINE (NHIK 3025).

Bakke O, Eik-Nes KB
Inst. Biophysics, Univ. Trondheim, 7034 Trondheim-NTH, Norway
J Cell Physiol; 109(3):489-496 1981

Cells, synchronized by mitotic selection, were exposed to dexamethasone (DEX) throughout the cell cycle. Cells exposed during the first half of G1 had lengthened cell cycle time, and most of the prolongation occurred in that phase. Exposure during other phases was ineffective. The growth inhibition was reversible, but did not extend to subsequent cell cycles where there was no exposure to DEX. (23 Refs)

7. SEPARATION OF BASAL HISTONE SYNTHESIS FROM S-PHASE HISTONE SYNTHESIS IN DIVIDING CELLS.

Wu RS, Bonner WM
Lab. Molecular Pharmacology, Developmental Therapeutics Program, NCI, Bethesda, MD, 20205
Cell; 27(2):321-330 1981

Histone synthesis in cycling tissue-culture cells can be separated into basal synthesis and S-phase synthesis. S-phase histone synthesis comprises about 90% of total histone synthesis, and in this regard our results support the generally held model that most histone synthesis is tightly linked to DNA synthesis. Basal histone synthesis is less than 10% of the S-phase synthesis but persists throughout the S, G2 and G1 phases of the cell cycle, while S-phase synthesis rises in parallel with the increase in DNA synthesis. Chinese hamster ovary cells, the H2A variants Z and X, and the H3 variant 3, participate in basal histone synthesis while the H2A variants 1 and 2, and the H3 variant 2, participate in S-phase histone synthesis. H2B and H4 participate in both kinds of synthesis. Because specific H2A and H3 variants are involved, basal histone synthesis cannot be attributed to contamination by cells in S-phase. Whole cells and isolated nuclei yield the same results. Basal histone synthesis can be demonstrated in cells synchronized by mitotic shake-off either alone or in combination with isoleucine starvation and colcemid blockage. It is also differentiated from S-phase histone synthesis by its relative insensitivity to hydroxyurea, indicating that basal histone synthesis is not linked or is at least less tightly linked to DNA synthesis. The basal H2A variants X and Z of five other cell lines all show similar relative insensitivities to hydroxyurea treatment. These lines include attached cultures, suspension cultures, a normal line and transformed lines from human, mouse, rat and Chinese hamster, indicating that basal histone synthesis may be a property of all cycling cells. The integration of basal histones into chromatin seems to follow the same pathway as S-phase histones, but the kinetics are somewhat slower. (Author abstract) (32 Refs)

8. EARLY CHANGES IN PHOSPHATIDYLINOSITOL AND ARACHIDONIC ACID METABOLISM IN QUIESCENT SWISS 3T3 CELLS STIMULATED TO DIVIDE BY PLATELET-DERIVED GROWTH FACTOR.

Habenicht AJ, Glomset JA, King WC, Nist C, Mitchell CD, Ross R (c/o Glomset) Regional Primate Res. Center SJ-50, Univ. Washington, Seattle, WA, 98195
J Biol Chem; 256(23):12329-12335 1981

We added platelet-derived growth factor to cultures of quiescent Swiss 3T3 cells to investigate early changes in lipid metabolism related to initiation of cell cycle traverse. In a series of experiments that focused on lipid degradation we added the growth factor to cells that had been prelabeled with myoinositol, glycerol, or arachidonic acid. We observed the following mitogen-dependent effects: a decline of radioactivity in cell phosphatidylinositol within 2 to 5 min that progressed to 25 to 50% during the 1st hr, a transient rise of radioactivity in cell diacylglycerol that peaked at 10 min, a gradual increase of radioactivity in monoacylglycerol in the medium, and a concomitant increase of radioactivity in medium-free fatty acid. In experiments that focused on lipid biosynthesis, we added the growth factor to cells and pulse-labeled them with radioactive precursors. We observed increased incorporation within 60 min of myoinositol into phosphatidylinositol, arachidonic acid into phosphatidylinositol, diacylglycerol, and phosphatidylethanolamine, and choline into phosphatidylcholine. These results support the possibility that action of platelet-derived growth factor on Swiss 3T3 cells leads to release of diacylglycerol from phosphatidylinositol, that some of the released diacylglycerol is hydrolyzed to monoacylglycerol and arachidonic acid, and that these lipid products are in part reconverted to phosphatidylinositol and other lipids. (Author abstract) (37 Refs)

9. IMMUNOLOGICAL DELINEATION IN NORMAL AND MALIGNANT CELLS OF A MEMBRANE PROTEIN INVOLVED IN GLUCOSE TRANSPORT. II. FUNCTION OF THE ANTIGEN.

Gingrich RD, Wouters M, Bramwell ME, Harris H
Sir William Dunn Sch. Pathology, South Parks Road, Oxford OX1 3RE, England
J Cell Sci; 52:121-135 1981

A review of the literature suggested that the antigen detected by the M/27 antibody described in the preceding paper might be involved in the transport of glucose across the cell membrane. This idea was tested by measuring the amount of M/27 antibody bound to cells under a range of conditions known to influence the rate of glucose uptake. Glucose starvation and the administration of insulin under appropriate conditions are known to increase the Vmax for glucose uptake in certain cells, and high cell density in vitro is known to decrease the Vmax. Glucose starvation was found to increase the amount of M/27 antigen present on the surface of two malignant cell lines, but produced no detectable change in five different non-malignant cell types. Insulin increased the amount of M/27 antigen on the surface of both malignant and non-malignant cells. At high cell density, the amount of M/27 antigen present on the cell surface decreased. The changes in the Vmax for glucose uptake produced by these manipulations have been shown not to requir e the synthesis of protein. This was also found to be true for the changes in M/27 antigen concentration. By disrupting cells in detergent, it could be shown that there was an intracellular pool of M/27 antigen. The total amount of M/27 antigen in the cell was found to be about 4x as large as the amount of the antigen on the cell surface. This

figure agrees with the value given in the literature for the size of the intracellular pool of the glucose transport system. The amount of M/27 antigen on the cell surface was found to vary during the cell cycle. A dramatic increase occurred early in S phase. (Author abstract) (31 Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

10. MONOCYTE-INDUCED CELL CYCLE SYNCHRONIZATION OF LEUKEMIC CELL LINE IN VITRO.

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Section Haematology and Immunology, Trondheim Regional Hosp., N-7000 Trondheim, Norway
Cytometry; 2(3):179-184 1981

The behavior of cells of human leukemic cell line K-562, cocultured with human monocytes for 24 hr and then separated, was studied by measuring the proliferation rate, the incorporation of methyl-3H-thymidine, and by evaluating phase distributions in the cell cycle by flow cytofluorometry. A partial, reversible blockage of the K-562 cell cycle in G0/G1 phase was observed. Within 1-3 days after separation of target cells from the monolayers of monocytes, the target cells regained their normal proliferation rate. Max numbers of cells in S-phase occurred at 7-9 hr after separation. Monocytes cultured in vitro for 12 days, and monocytes stimulated by addition of lymphokine (supernatants from BCG-exposed lymphocyte cultures) to their culture, caused the most pronounced blockage effect on K-562 cell division. (23 Refs)

11. CHARACTERIZATION OF PROLIFERATIVE AND QUIESCENT LEUKEMIC CELLS BY FLOW CYTOMETRY.

Preisler HD, Darzynkiewicw Z
Dept. Medical Oncology, Roswell Park Memorial Inst., Buffalo, NY, 14263
J Med; 12(6):415-425 1981

Leukemic cells obtained from the peripheral blood and bone marrow of two patients were separated into kinetically active and kinetically quiescent subpopulations by centrifugal elutriation. The subpopulations of cells were compared to each other and to the parent populations by means of flow cytometry and autoradiography. The larger kinetically active subpopulation differed from the original unseparated cells and from the small cell population in containing a larger amount of RNA and having a greater proportion of cells in late G1. Subpopulations of large and equivalently sized cells obtained from the bone marrow and peripheral blood were compared and despite essentially identical size distributions the marrow cells were more kinetically active. (Author abstract) (11 Refs)

12. DNA CONTENT AND KINETIC CHARACTERISTICS OF NON-HODGKIN'S LYMPHOMA: DETERMINED BY FLOW CYTOMETRY AND AUTORADIOGRAPHY.

Costa A, Mazzini G, Del Bino G, Silvestrini R
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Cytometry; 2(3):185-188 1981

Samples of malignant lymph nodes obtained from 74 non-Hodgkin's lymphoma (NHL) patients were cultured; DNA content and 3H-thymidine labeling index (LI) were determined. Propidium iodide was the DNA-specific fluorescence dye used in cytofluorography. Ploidy was expressed as the ratio of relative DNA content of human lymphoid G0/1 cells to that of chicken red blood cells. Of the NHL, 45/74 (61%) were aneuploid, and 91% of those showed a hyperdiploid DNA content. The max frequency of aneuploid tumors (72%) in comparison to diploid tumors (28%) was found in the group with unfavorable histology (original Rappaport classification), but the observation was not significant. Tumors with high proliferative activity showed a significantly (p less than 0.01) lower percentage of cells in G0/1 and a higher percentage of cells in S (P less than 0.01) than those with low proliferative activity. An analysis of 21 cases with a homogenous cell population indicated that the S phase fractions, as determined by cytofluorometry and autoradiographic LI, are correlated (r = 0.95, p less than 0.01). (19 Refs)

13. A NUCLEAR ANTIGEN ASSOCIATED WITH CELL PROLIFERATION AND BLAST TRANSFORMATION. ITS DISTRIBUTION IN SYNCHRONIZED CELLS.

Takasaki Y, Deng JS, Tan EM
Div. Rheumatic Diseases, Dept. Medicine, Univ. Colorado Sch. Medicine, Denver, CO, 80262
J Exp Med; 154(6):1899-1909 1981

The time relationship of nuclear antigen present in proliferating cells (PCNA) to synthesis of DNA, RNA, and protein during the cell cycle was examined. Two sera (EB and MN) from patients with systemic lupus erythematosus contained precipitating anti-PCNA antibody along with antibodies to other nuclear antigens. Insolubilized rabbit kidney extract was used as an immunoadsorbant; precipitating antibodies to other nuclear antigens were removed with the exception of anti-PCNA. WiL-2 diploid human B lymphocytes were examined with EB-absorbed serum at different phases of synchronized growth. At G0, immediately after release from density-dependent arrest, PCNA were present as speckled nucleoplasmic staining. At 12 hr, nucleolar staining and speckled nucleoplasmic staining were evident. At 20 hr, nucleolar staining had disappeared from most cells, but speckled nucleoplasmic staining was strong. In mitosis, staining was more intense in areas peripheral to chromosome condensation, but radiating strands of staining could be seen within the region of chromosome condensation. In WiL-2 cells, nucleolar staining predominated in a period which overlapped late G1 and early S, while in phytohemagglutinin-stimulated lymphocytes, nucleolar stain ing was the dominant pattern well before DNA synthesis occurred. Results demonstrate that the relationship of PCNA to proliferation and blast transformation may be associated with events related to DNA synthesis in the cells. (14 Refs)

14. A SPECIFIC BIOSYNTHETIC MARKER FOR IMMATURE THYMIC LYMPHOCYTES.

Rothenberg E
Dept. Cancer Biology, Salk Inst., San Diego, CA, 92138
J Exp Med; 155(1):140-154 1982

This study was designed to search for patterns of gene expression that distinguish the proliferating cells in the thymus from the majority populations of both the cortex and medulla. A combination of centrifugal elutriation and differential binding to peanut-agglutinin (PNA)-coated plates was employed to obtain a high yield of large cortical thymocytes from C57BL/6-Tla mice. The lymphoblastic-rich fractions consisted of cells which were clearly distinct from the great majority of the thymocytes with an av rate of [35S] methionine incorporation per

cell which was 20x higher than that of the majority population. 70% were in the S or G2 + M phases of the cell cycle. Cells that bound to PNA synthesized high levels of Lyt2/3 which confirmed their identity as cortical thymocytes, while those that failed to bind made little or no Lyt2/3 suggesting that these might be medullary cells. The fraction that bound to PNA was also enriched in cortical thymocyte precursors. The thymus-leukemia antigen glycoprotein was produced actively in fractions containing dividing cells suggesting that it is made at a narrowly circumscribed stage of early thymocyte development that correlates with rapid proliferation. (60 Refs)

15. EXPRESSION OF ERYTHROID DIFFERENTIATION AND TERMINAL CELL DIVISION IN INDUCED FRIEND LEUKEMIA CELLS.

Gambari R, Marks PA, Rifkind RA, Farace M, Fantoni A
Istituto di Biologia Generale, Universita di Roma, Roma, Italy
Acta Biol Med Ger; 40(4/5):511-518 1981

The relationship between cell cycle and globin gene expression was investigated during late differentiation of Friend leukemia cells (FLC) treated with hemin. Cell growth and cell cycle kinetics in the FLC line DS19 were determined by propidium iodide staining and by flow microfluorometry analysis of relative DNA content. Globin gene expression was studied by molecular hybridization of phenol extracted cytoplasmic RNA with mouse globin (3H)-complementary (c)DNA or by cDNA cellulose chromatography of pulse-labeled (3H)RNA purified from the nuclei or cytoplasm of FLC cultured with the inducer hexamethylenebisacetamide (HMBA) or hemin. In FLC treated with HMBA, accumulation and translation of globin messenger (m)RNA and Hb were associated with terminal cell division. Since hemin did not induce expression of genes responsible for terminal cell division, the relationship between cell cycle and globin gene expression was det ermined during late differentiation of FLC treated with hemin. Results demonstrate that terminal cell division does not necessarily occur in cells which accumulate both globin mRNA and Hb, suggesting that these features are not necessarily coupled in leukemia erythroid differentiation. (14 Refs)

CELL CYCLE - SPECIFIC PHENOMENA

16. EFFECT OF N-BUTYRATE ON CELL CYCLE PROGRESSION AND IN SITU CHROMATIN STRUCTURE OF L1210 CELLS.

Darzynkiewicz Z, Traganos F, Xue SB, Melamed MR
Memorial Sloan-Kettering Cancer Center, New York, NY, 10021
Exp Cell Res; 136(2):279-293 1981

In the presence of 1-5 mM n-butyrate, murine leukemic L1210 cells cease proliferation and become arrested in the G1A compartment of the G1 phase. Cells in this compartment are characterized by low RNA content and more condensed chromatin. During unperturbed growth the cell residence times in G1A are of indeterminate duration. The effect of n-butyrate in arresting cells in G1A was concentration-dependent. However, the sensitivity of L1210 cells to this drug was markedly enhanced when cells were treated for longer than one generation (12 hr). Cells arrested in G1A remained viable and when n-butyrate was removed, after a lag period, they resumed progression through the cycle. The effect of n-butyrate on cell progression through various parts of the cycle was studied in a stathmokinetic experiment. DNA in situ in nuclei of n-butyrate-treated cells had lowered (by 2-8 C) stability to thermal denaturation and increased (by 15%) accessibility to DNase I. DNA in situ in the nuclei of n-butyrate-treated cells also showed decreased sensitivity to acid-induced denaturation. Changes in chromatin were seen in all cells, regardless of cell cycle phase, within the first hr after addition of n-butyrate. Mitotic cells, however, reacted to n-butyrate more rapidly than interphase cells. The observed changes in L1210 cells are most likely a consequence of histone modifications (acetylation of inner histones, dephosphorylation of histone H1) induced by n-butyrate. (41 Refs)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

17. EFFECTS OF THIOTEPA ON PRIMARY CULTURES OF DMBA-INDUCED MAMMARY TUMOURS OF RATS: KINETICS AND ULTRASTRUCTURE.

Fink SM, Tseng MT
Dept. Anatomy, Univ. Louisville, Louisville, KY, 40292
Br J Cancer; 44(5):762-765 1981

Effects of thiotepa (TP) on growth kinetics, thymidine labeling index (LI), and fine structure of cells cultured from mammary tumors induced by 7,12-dimethylbenz(alpha)anthracene (DMBA) in female Sprague-Dawley rats were determined. Cell subpopulations of these tumors were separated by isopycnic centrifugation. Primary cell cultures were obtained from band 3. Of the three parameters measured, the most obvious TP (10(-2) 10(-6) M)-induced changes were in the rate of DNA synthesis as determined by LI. At 10(-2) M TP, none of the remaining attached cells incorporated (3H)thymidine during pulse labeling. While the percentage of cells in S phase closely approximated the percentage of attached cells after treatment with 10(-6) M TP, the LI curve declined more sharply than the dose-response curves. Ultrastructural analysis revealed no viable cells remaining after 10(-2) M TP. At the lowest TP concentration (10(-6) M), the cells could not be distinguished from controls on the basis of fine structure. Cell-kinetic data indicated that growth inhibition of the selected DMBA-induced tumor cell subpopulation in culture by TP is dose-dependent. A good correlation was found between cell kinetics and labeling index. Indirectly, the study supports the concept of cell heterogeneity in solid tumors. (9 Refs)

18. CYTOKINETIC BEHAVIOR OF EHRLICH ASCITES TUMOR AFTER IN VIVO TREATMENT WITH CIS-DIAMMINEDICHLOROPLATINUM(II) AND METALLOCENE DICHLORIDES.

Kopf-Maier P, Wagner W, Liss E
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J Cancer Res Clin Oncol; 102(1):21-30 1981

The influence of an in vivo treatment with optimally tumor-inhibiting doses of cis-diamminedichloroplatinum(II) (DDP), titanocene dichloride (TDC), and vanadocene dichloride (VDC) on the DNA distribution pattern, determined by pulse-cytophotometry, and on the mitotic activity of EAT cells is investigated. Whereas DDP causes an immediate and long-lasting decrease of mitoses but no disturbances of the EAT cell kinetics, a marked G2 block with a maximum at 10-12 hr a t and an irreversible and extensive mitotic depression is evoked by

TDC. In the case of DDP and TDC, the tumor cells are removed several days a t by cells belonging to the defensive system of the host animals. In contrast, VDC induces partially synchronized waves after a transient suppression of mitoses and reversible cell accumulation in the late S and in the G2 phases. Additionally, 5-16% of the cells become polyploid after VDC treatment. (Author abstract) (17 Refs)

19. ANTIPROLIFERATIVE ACTIVITY OF PROTOCATECHUALDEHYDE ON CHINESE HAMSTER CELLS GROWN IN CULTURE.

Nishimura M, Umeda M, Kusanagi A, Urakabe R, Yukimatsu K, Otawara S
Tissue Culture Lab., Yokohama City Univ. Sch. Medicine, 2-33, Urafunecho, Minami-ku, Yokohama 232, Japan
Gan; 72(6):868-879 1981

The mode of cytotoxic action of protocatechualdehyde on V79 cells was examined. The cytotoxicity of protocatechualdehyde on V79 cells was time- and cell cycle-dependent. The lethal action is selective for the cells at S phase only. The cells lethally damaged at S phase seemed to complete their DNA synthesis, although the rate of DNA synthesis became lower and the duration of S phase was prolonged. Some cells arriving at G2 phase directly entered the next S phase without cell division and died of karyor rhexis or karyolysis. Cells treated at stages of the cell cycle other than S showed normal progression of their cell cycle to the G1/S boundary. The block point of the cell cycle seemed to lie a little behind that with hydroxyurea. When the cells at phases other than S were blocked with protocatechualdehyde for 14 hr, elongation of the next S phase occurred after removal of protocatechualdehyde. On alkaline sucrose gradient analysis, little scission of parental DNA was observed in the cells treated with protocatechualdehyde. (Author abstract) (12 Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

20. G2-DELAY AFTER IRRADIATION WITH ALPHA-PARTICLES AS STUDIES IN SYNCHRONIZED CULTURES AND BY THE BROMODEOXYURIDINE-33258H TECHNIQUE.

Hieber L, Beck HP, Lucke-Huhle C
Nuclear Research Center Karlsruhe, Inst. Genetics and Toxicology, D-7500 Karlsruhe 1, W. Germany
Cytometry; 2(3):175-178 1981

Mouse fibroblasts, strain L-929, were grown as monolayers, both asynchronously and synchronized by serum deprivation. The fibroblasts exhibited a pronounced lengthening of the G2 phase when exposed to 4 million electron volt (MeV) alpha-particles from an Am-241 source (irradiation at 10(4) cells/square cm). Dose rate at the cell surface was 0.35 Gy/min and the energy of the particles was 3.4 MeV, yielding an alpha particle efficiency of 120 kilo electron volt/micrometer. DNA distributions were analyzed by flow cytometry using either cytofluorography or the bromodeoxyuridine-33258 Hoechst technique using the Phywe ICP 22 detector. Delays in division were longest for cells irradiated in G2 or at the G1/S border and were least affected for exposure during the G1 phase. The dose dependency of the G2 delay was linear in the lower dose ranges but showed a break at higher doses. (18 Refs)

21. TURNOVER OF PROLIFERATIVE CELLS IN THE SPINAL CORD AFTER X IRRADIATION AND ITS RELATION TO TIME-DEPENDENT REPAIR OF RADIATION DAMAGE.

Hornsey S, Myers R, Coultas PG, Rogers MA, White A
MRC Cyclotron Unit, Hammersmith Hosp., London W12 0HS, England
Br J Radiol; 54(648):1081-1085 1981

The changes in labelling index of neuroglial cells of the rat cervical cord following 20 Gy X rays are compared with the timing and pattern of the repair of radiation damage in the spinal cord. The start of time-dependent repair coincides with the release of the proliferative neuroglia from a block at the G1/S border. The evidence suggests that the time-dependent repair effects the normal unstimulated proliferation of the surviving neuroglial cells and that homeostatically stimulated recruitment to the proliferative neuroglia does not occur until the period just before the development of paralysis. A normal cell-cycle time of about one month for the spinal cord neuroglia is indicated from the observed pattern o f labelling. (Author abstract) (13 Refs)

22. EARLY CHANGES IN THE RADIOSENSITIVITY OF CORYNEBACTERIUM PARVUM-STIMULATED CFU-S.

Maruyama Y, Grider C
Dept. Radiation Medicine, Univ. Kentucky Medical Center, Lexington, KY, 40536
Stem Cells; 1(2):81-96 1981

Corynebacterium parvum injected ip into C57BL mice induced a progression of hemopoietic CFU-S of C57BL mice from the resting state immediately after, and in the early period (approx 8 hr) after stimulation. Dose-response survival curves were determined for resting, 4 hr C parvum-stimulated, and then 'suicided' with high specific-activity tritiated thymidine (HSATT), and 6 hr cells exposed to vinblastine (VBL) and HSATT i hr before radiation. Dose-response survival curves of the stimulated endogenous spleen CFU-S after the injection revealed changing slopes or dose to reduce survival by 0.37 on the linear curve (D0) of dose-response curves indicative of changing sensitivity states. Shortly after stimulation with C parvum injection the sensitivity of cells indicated that they were in the DNA-S phase. D0 survival curve slope changes reflect radiosensitivity changes. Sensitivity increased shortly after injection, but at about 6 hr sensitivity to HSATT disappeared and the radiosensitivity increased. Sensitivity to VBL became evident at 7 hr with the begining of mitosis and mitotic sensitivity to VBL. A dose-response survival curve for the G2 phase CFU-S was determined using both HSATT and VBL to eliminate the DNA-S phase and mitotic cells. G2 sensitivity showed a complex bending dose-response curve with a terminal D0 of 58 rad. The D0 values indicate that D0 for resting endogenous CFU-S was 80 rad, for the DNA-S phase 105 rad, and for the late G1-early S phase 85 rad. The radiosensitivities were measured in vivo. CFU-S progression was blocked by metiamide the anti-histamine H2 receptor agent. (27 Refs)

23. PHOTODYNAMIC EFFECTS OF HAEMATOPORPHYRIN DERIVATIVE ON SYNCHRONIZED AND ASYNCHRONOUS CELLS OF DIFFERENT ORIGIN.

Christensen T, Feren K, Moan J, Pettersen E
Dept. Biophysics, Norsk Hydro's Inst. Cancer Res., Montebello, Oslo 3, Norway
Br J Cancer; 44(5):717-724 1981

Phototherapy in the presence of hematoporphyrin derivative has been shown to have a preferential effect on malignant tumors when compared to normal tissue. This communication presents a comparison of the sensitivity to photochemotherapy in vitro of different cell lines. Asynchronous populations of cells were exposed to light in the presence of hematoporphyrin derivative, and found to be inactivated with a comparable efficiency. The lines were of human, Chinese-hamster or mouse origin and had different abilities to form tumors after heterotransplantation into nude mice or transplantation into syngeneic, immunosuppressed mice. Synchronized cells from four of the lines showed a similar variation in sensitiv ity to light throughout the cell cycle. Cells near the middle of interphase showed the highest sensitivity, whilst cells in early G1 were found to be least sensitive towards treatment with hematoporphyrin derivative and light. (Author abstract) (40 Refs)

24. A COMPARISON OF THE RESPONSE TO HYPERTHERMIA OF MURINE HAEMOPOIETIC STEM CELLS (CFU-S) AND L1210 LEUKAEMIA CELLS: ENHANCED KILLING OF LEUKAEMIC CELLS IN PRESENCE OF NORMAL MARROW CELLS.

Symonds RP, Wheldon TE, Clarke B, Bailey G
Radiobiology Res. Group, Glasgow Inst. Radiotherapeutics and Oncology, Belvidere Hosp., Glasgow G32, Scotland
Br J Cancer; 44(5):682-691 1981

When the clonogenic survival of mouse hemopoietic stem cells (CFU-S) and leukemia L1210 cells grown as ascites tumors are compared after being heated in vitro and assayed in vivo by spleen-colony assay, there is no significant difference in the terminal slopes of the survival curves. The shoulders of the survival curves differ, but this may be explained by differences in cell kinetics. By contrast, L1210 leukemic marrow cells are considerably more susceptible to the lethal effects of hyperthermia (43 C) than either normal marrow stem cells or L1210 leukemic cells grown as ascites tumors. Moreover, the killing of L1210 ascites cells by hyperthermia can be enhanced by heating L1210 ascites cells with an equal number of normal marrow cells, or a supernatant removed from heated marrow cells. Most cells in leukemic marrow are normal, and it is postulated that the increased thermal sensitivity of L1210 cells in leukemic marrow is caused by diffusible factors (eg lysosomal enzymes) released by heating normal marrow cells. (Author abstract) (25 Refs)

25. EFFECT OF HYPERTHERMIA ON CHO DNA POLYMERASES ALPHA AND BETA.

Spiro IJ, Denman DL, Dewey WC
Dept. Oncology, George Washington Univ. Medical Center, Washington, DC, 20037
Radiat Res; 89(1):134-149 1982

Loss of polymerase beta (pol-B) activity assayed in Chinese hamster ovary (CHO) cell extracts following thermal treatment of whole cells was examined. Pol-B activity decreased progressively as the treatment temperature was increased from 42.2 to 45.5 C. At temperatures of 43 C and greater, activity loss was exponential as the duration of treatment was lengthened. The heat sensitivities of pol-B and polymerase alpha (pol-A) were compared at 45.5, 43.5, and 42.3 C. At the two higher temperatures, pol-A was considerably more heat stable than pol-B with greater than 10% of the pol-A activity remaining after a 35-min heat dose at 45.5 C. The heat sensitivities of pol-A and pol-B were identical when cells were treated at 42.3 C. Pol-B activity was shown to be more sensitive to combinations of heat and procaine-HCl than to heat alone. The heat inactivation rates for synchronous G1-and S-phase cells were the same and identi cal to rates for asynchronous cells, although the absolute level of pol-B is higher in S-phase cells than in G1 cells. No diffusible factor was produced by heated CHO cells which could cause inhibition of pol-B by transfer to the unheated sample. The return of pol-B activity following heating is described. Inhibition of unscheduled DNA synthesis (UDS) correlated very well with loss of pol-B activity. The data demonstrate that the loss of intracellular pol-B activity correlates with heat killing, heat radiosensitization, and a reduction in repair capability as measured by UDS. (64 Refs)

OTHER RELATED STUDIES

26. EFFECTS OF RETINOIC ACID AND TUMOR PROMOTER 12-O-TETRADECANOYLPHORBOL-13-ACETATE (TPA) ON THE CELL CYCLE OF HELA CELLS.

Kinzel V, Krombholz-Nolinski I, Stohr M, Richards J
German Cancer Res. Center, Inst. Experimental Pathology, Im Neuenheimer Feld 280, D-6900 Heidelberg, W. Germany
Int J Cancer; 29(1):93-99 1982

The influence of retinoic acid (RA), a modifier of tumor promotion, on the cell cycle of HeLa cells, and its ability to interfere with the early irradiation-like effects induced by the tumor promoter 12-O-tetradecanoylphorbol-13-acetate (TPA) has been investigated by a variety of different techniques. These include measurement of thymidine incorporation and uptake, of labeling and mitotic indices, and of DNA histograms by flow cytometry. Within 24 hr RA (2 x 10(-5) M) alone caused a short-lasting inhibition of DNA synthesis; later a decrease of cells in S phase and a steady descending mitotic activity were observed. On combined treatment with RA and TPA (10(-8) M), the latter seems to dominate RA in two instances: (1) the transient G2 blockage due to TPA is seen as the earliest effect; however, the cultures do not seem to recover as well if RA is also present; (2) the TPA-induced GI blockage appears to be effective but less pronounced in the presence of both chemicals. Where the third typical TPA-induced effect is concerned, however, both compounds seem to act to a comparable degree in the same time frame; namely by an initial inhibition of DNA synthesis which thus might be a point of critical interference if promoter and modifier are given together. (Author abstract) (44 Refs)

27. SISTER CHROMATID EXCHANGE INDUCTION AND CELL CYCLE INHIBITION BY ANILINE AND ITS METABOLITES IN HUMAN FIBROBLASTS.

Wilmer JL, Kligerman AD, Erexson GL
Dept. Genetic Toxicology, Chemical Industry Inst. Toxicology, P.O. Box 12137, Research Triangle Park, NC, 27709
Environ Mutagen; 3(6):627-638 1981

The effects of aniline HCL, para-aminophenol (pAP), ortho-aminophenol (oAP), acetanilide (AA), para-hydroxy-acetanilide (pOHAA), ortho-hydroxyacetanilide (oOHAA), and N-phenyl-hydroxylamine (PHA) on sister chromatid exchange (SCE) and cell proliferation were investigated in human fibro blasts. Although considerable diversity in cytological effects was observed, oAP and PHA were the only compounds found to induce dose-dependent increases in SCE. With 0.1 milliM (mM) oAP the SCE frequency was doubled; at 0.1 mM PHA the SCE frequency was increased 40% over controls. PHA appeared to inhibit cell proliferation to a greater extent than oAP. A slowing of the cell cycle was observed with 0.01 mM PHA and with 0.1 mM oAP. Concentrations of 0.5 mM PHA and 0.3 mM oAP caused extensive cell death. Aniline HCL induced minimal but significant increases in SCE. On the basis of SCE frequency per millimole, oAP was approx 3.1x more potent than PHA; PHA was approx 87.4x more potent than aniline HCl. pOHAA (10 mM) induced pronounced inhibition of cell replication but no increases in SCE. Determination of mitotic indices proved to be far less sensitive as an indicator of toxicity than cell cycle analysis. (56 Refs)

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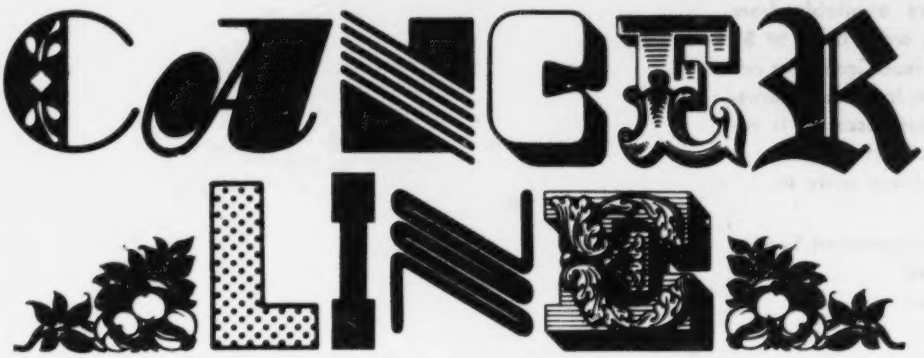

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KINETIC METHODS AND MODELS

1. CRYOPRESERVATION AND SUBSEQUENT VIABILITY OF HUMAN BONE MARROW IN HEMATOLOGIC MALIGNANCIES: COMPARISON OF TWO DIFFERENT METHODS OF CELL RECONSTITUTION.

Porcellini A, Manna A, Manna M, Moretti L, Agostinelli F, Lucarelli G
Divisione di Ematologia, USL-3, Ospedale di Pesaro, Pesaro, Italy
Cryobiology; 18(6):541-546 1981

Bone marrow cells collected from patients with hematologic malignancies were cryopreserved using DMSO as a cryoprotective agent. The growth kinetics of hemopoietic stem cells

HE 20.3172/2

frozen to-196 C was monitored immediately after thawing by the semisolid agar CFU-C assay and two different methods of cel l reconstitution were compared. In the first procedure, thawed cells were plated after the removal of DMSO by washing the cell suspension; in the second, cell suspensions were cultured after a simple 1:1 dilution of DMSO with medium. The numbers of CFU-C per 2 x 10(5) cells plated was higher by washing out the DMSO in all the groups studied. However, the absolute numbers of CFU-C contained in the whole ampules after the freezing procedures was approx the same using both methods. It is concluded that washing the cells only apparently yielded a better cloning efficiency, suggesting that such a procedure led to a higher mature nucleated cell loss with the consequence of a CFU-C concentration. This trend seems particularly evident in cells from the AML and CML patients. (Author abstract) (19 Refs)

2. CELL-KINETIC AND GENETIC CHARACTERIZATION OF SQUAMOUS EPITHELIAL CARCINOMAS OF THE HEAD AND NECK.

Muller RP, Addicks HW, Gohde W, Schumann J
Radiologische Klinik der Universitat, Jungeblodtplatz 1, D-4400 Munster, W. Germany
Dtsch Zahnaerztl Z; 36(11):693-696 1981

Analysis of epithelial carcinomas of the head and neck by impulse cytophotometry (IC) is described. Tumor tissues samples obtained by excision or needle biopsy are worked up immediately after removal; samples may be fresh or fixed in 70% methanol or ethanol. Results can be obtained within 10-15 min after removal of the sample from the patient. IC produces a histogram containing information about ploidy stages of cells in the sample. The mean chromosome number for the sample is calculated using a computer program. From IC the proliferative activity of the sample, indicated by the fraction of cells in the S-phase, is determined. Normal tissue consists mainly of diploid cells; the fraction of normal cells with higher DNA content usually does not exceed 10%. Various tumor types such as melanoma, squamous epithelial carcinoma, testicular tumors, and sarcomas are aneuploid in 80-100% of cases. S-phase cells in tumor tissue can account for as much as 25% of the total cell population (up to 50% for solid tumors). Although data for in vivo tumors are not available, evidence indicates that the radiosensitivity of tumors is related to proliferative activity. Thus IC provides a quick method for determining tumor radiosensitivity for a minimal expenditure of time and money. (14 Refs) (In GER)

3. FLOW MICROFLUOROMETRIC ANALYSIS OF CELL CYCLE PARAMETERS IN EXPONENTIALLY GROWING CELL POPULATION (MEETING ABSTRACT).

Watanabe I
Division Physiology and Pathology, National Institute Rad Science, Chiba, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

Although flow microfluorometric analysis made it possible to estimate the fraction of cells in each phase of cell cycle, no parameter on time required by the cells to pass each phase was obtained. To overcome the weak point, Descrete Time Kinetic model was proposed by Beck (1978). The model, however, require a large amount of mitotic cells selectively harvested from an exponentially growing cell population. A new method, presented here, requires only several exponentially growing samples to estimate generation time, duration of G1, S, G2, and M phases in the cell cycle. Simultaneously, fractions of G2 and M phase cells also be estimated by this method. The principle of the method was based on time-dependent reduction of G1 and accumulation of G2+M phase cells in the presence of Colcemid. We tested this method for mouse leukemic L5178Y, human carcinoma HeLa S3, and human malignant melanoma HMV-1 cells and obtained satisfactory results. (no Refs)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

4. SYNTHESIS OF ALPHA-FETOPROTEIN (AFP) AND CELL PROLIFERATION IN REGENERATING LIVERS OF NMRI MICE AFTER PARTIAL HEPATECTOMY: AN IMMUNOHISTOCHEMICAL AND AUTORADIOGRAPHIC STUDY WITH 3H-THYMIDINE.

Tuczek HV, Fritz P, Wagner T, Braun U, Grau A, Wegner G
Dept. Clinical and Experimental Pathology, Robert-Bosch-Hosp., Auerbachstrasse 110, D-7000 Stuttgart 50, W. Germany
Virchows Arch [Cell Pathol]; 38(2):229-237 1981

To get more information concerning the relation between cell proliferation and the synthesis of alpha-fetoprotein (AFP), liver regeneration and AFP production was followed simultaneously in short intervals in NMRI mice after two-thirds hepatectomy using autoradiographic and immunohistochemical methods. The results indicate that AFP synthesis is not linked closely to cell proliferation in the sense that each proliferating hepatocyte synthesizes AFP during a definite phase of the cell cycle. However, AFP production, as measured by the index of anti-AFP positive hepatocytes, occurs in a very small population of parenchymal cells when the bulk of the hepatocytes has just passed the S-phase and is considered to be in the G2-, M or early G1-phase of *the cell cycle* when the cells are still in an undifferentiated state. (Author abstract) (58 Refs)

5. DNA CHARACTERISTICS OF HUMAN PITUITARY TUMOURS.

Anniko M, Holm LE, Tribukait B, Werner S
Dept. Otolaryngology, Karolinska Hosp., S-104 01 Stockholm, Sweden
Acta Otolaryngol [Suppl] (Stockh); (379):5-11 1981

Biopsies from pituitary tumors in eight patients were analyzed with DNA flow-cytofluorometry immediately after surgery and after organ culture. Good agreement was found between the degrees of ploidy and of the relative proportions of cells in different phases of the cell cycle, indicating a good stability and reproducibility of pituitary tumor explants in vitro. Analysis of DNA content in dicated a homogeneous cell population in tumors before and after explanation. No apparent correlation was observed between hormone secretion rate in diploid and aneuploid tumors, respectively, and DNA characteristics. (Author abstract) (19 Refs)

6. GROWTH RATES OF SMALL CELL ANAPLASTIC LUNG CANCER (SCACL): DIFFERENCES WITH SITE/ SUBTYPE (MEETING ABSTRACT).

Brigham BA, Bunn PA, Matthews MJ, Dahaba N
No affiliation given
Clinical Oncology Society of Australia, November 24-27, 1981, Melbourne, Australia. The Society 70 pp., 1981.

Fine needle aspirates, biopsies and bronchial washings were used in a labelled thymidine uptake study of SCACL. A total

of 15 specimens were suitable for this study. Correlations with vol doubling times were made to demonstate the inaccuracies of potential doubling time calculations. Wide ranges in labelling index (LI), and labelling intensities were found, which reflected the heterogeneity between tumors. Differences between the subtypes were present with the intermediate-cell subtype showing a higher LI than the lymphocyte-like subtype. Additionally there was a difference in median grain counts of primary and metastatic lesions, suggesting more rapid proliferation of cells within metastases. This and the rapid growth rate demonstrated in the small cell number of vol doubling times of metastatic lesions, suggest metastases in SCACL may grow more rapidly than the primary tumor. These findings may explain site differences in response and relapse rates that have been reported for SCACL. (no Refs)

7. MORPHOLOGICAL CHARACTERISTICS OF TUMOR EXPLANTS CULTURED IN THE DIFFUSION CHAMBERS.

Iakhimovich LV, Semenova-Kobzar' RA, Umanskii IuA
Dept. Immunology of Carcinogenesis, Inst. Problems in Oncology, Kiev, USSR
Tsitologiia; 23(11):1304-1308 1981

Kinetics of proliferation and morphological characteristics of human tumor explants cultured in the diffusion chambers were studied. Surgery specimens of squamous cell carcinoma of the esophagus, adenocarcinoma of the rectum bronchogenic adenocarcinoma of the lung, and squamous cell carcinoma of the lung were cultured in the diffusion chambers implanted into the abdominal cavity of mice for 3-21 days. Cytological examination of tumor explants showed progressive proliferation of both epithelial and fibroblastlike cells. Fibroblastlike cells were located in the center of the filter, while epithelial cells formed layers of various density near the edge of the filter. The rate of proliferation and the ratio of epithelial and fibroblastlike cells depended upon the type of the tumor. (18 Refs) (In RUS)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

8. RESTRICTION POINT CONTROL OF CELL GROWTH BY A LABILE PROTEIN: EVIDENCE FOR INCREASED STABILITY IN TRANSFORMED CELLS.

Campisi J, Medrano EE, Morreo G, Pardee AB
(c/o Pardee), Sidney Farber Cancer Inst., 44 Binney St., Boston, MA, 02115
Proc Natl Acad Sci USA; 79(2):436-440 1982

It has been proposed that animal cells must accumulate a labile protein(s) before they can pass the restriction (R) point in the G1 phase of the cell cycle. Here, we present evidence that this R protein acquires increased stability in transformed 3T3 cells, thereby allowing these cells to continue growth under conditions that arrest untransformed cells. Low doses of cycloheximide or histidinol drastically reduced the rate at which normal 3T3 (A31) fibroblasts in early G1 could enter DNA synthesis. These drugs had less effect on entry of two tumorigenic A31 derivatives, BPA31 and SVA31, into S, although measurement of [3H]leucine incorporation showed that the inhibitors were equally effective in the three cell lines. The hypothesis is that the transformed lines are less sensitive because moderate inhibition of their R protein synthesis is compensated by lower rates of protein degradation. To test this idea, we completely inhibited cytoplasmic protein synthesis for several hours shortly before A31 and BPA31 cells had reached the R point. After removal of inhibitor, A31 cells showed delays in the onset of S that were in excess of the inhibitor pulse, consistent with decay of labile protein during the pulse. BPA31 cells showed no excess delays, suggesting a much more stable R protein. The half-life of the R protein was estimated at 2.5 hr in A31 cells, indicating that, in these cells, R protein synthesis starts at the beginning of G1. In the BPA31 cells the R protein showed no signs of decay for at least 8 hr. (Author abstract) (26 Refs)

9. MAMMALIAN CELL PROLIFERATION IS REGULATED BY THE SYNERGISTIC ACTIONS OF MULTIPLE GROWTH FACTORS.

Pledger WJ, Hart CA, Wharton WR
Dept. Pharmacology and Cancer Res. Center, Univ. North Carolina Medical Sch., Chapel Hill, NC, 27514
Adv Exp Med Biol; 138:287-300 1982

Regulatory events in the G1 phase of the mammalian cell cycle, regulation by serum factors and the process by which the transformation alters the normal regulation were studied. Mechanisms of action can be investigated after the growth factors and their ordered requirement in cell cycle traverse is learned. Comparison of the normal cells to transformed cells can lead to the understanding of how transformed or neoplastic cells override growth dependency on mitogenic signals. (18 Refs)

10. THE GROWTH INHIBITION IN FRIEND ERYTHROLEUKEMIA CELLS INDUCES CYCLING OF PREEXISTING NONHISTONE PROTEINS.

Yancheva N, Djondjurov L
Institut po Molekularna Biologia, Bulgarska Akademiya na Naukite, BG-1113 Sofiya, Bulgaria
Eur J Biochem; 121(2):309-316 1982

The present investigation performed on Friend erythroleukemia cells provides evi dence that the cellular reprogramming associated with transition of the cells from the growing to the resting state is accompanied by an intranuclear cycling of preexisting proteins migrating from the cytoplasm. The model system developed for this study affords an opportunity to follow these events in a conveniently short period. The flow microfluorometric analysis revealed that, with respect to DNA content, the quiescent nuclei exhibit distribution in G1, S and G2 phases, as do the nuclei of the control, exponentially growing cells. It was found further that the induction of quiescence arouses two waves of migration of preexisting cytoplasmic proteins toward the nucleus: an early one, during the transition to quiescence clearly showing density dependence, and a later one, in the established resting state. While the early-cycled proteins are undetectable in mass and once they have reached the nucleus have a short life time and, thus, could be considered as regulatory molecules, the late-cycled proteins accumulate within the nucleus and are associated most probably with structural reorganization of the resting nuclei; moreover, the late-cycled nonhistone proteins were found localized, at least partly, in the nuclear protein matrix structure. Control experiments confirmed that the early and late-cycled proteins have been synthesized in the cytoplasm in the proliferative state but are cycled intranuclearly only if the resting state has been induced. When finally the resting cells were stimulated to proliferate, the accumulated presynthesized and newly synthesized nonhistone proteins undergo a rapid degradation which sug-

gests that the new cellular program may require a complete elimination of the 'resting' nonhistone proteins. (Author abstract) (45 Refs)

11. SISTER-CHROMATID EXCHANGES AND CELL-CYCLE DELAY IN CHINESE HAMSTER V79 CELLS TREATED WITH 9 ORGANOPHOSPHORUS COMPOUNDS (8 PESTICIDES AND 1 DEFOLIANT).

Chen HH, Sirianni SR, Huang CC
Dept. Experimental Biology, Roswell Park Memorial Inst., Buffalo, NY, 14263
Mutat Res; 103(3-6):307-313 1982

Rapidly growing Chinese hamster V79 cells, pretreated with 5-bromodeoxyuridine (10 ug/ml), were treated with nine organophosphorus compounds in doses ranging from 10-80 ug/ml or 2.5-20 ug/ml. Significant increases in sister-chromatid exchanges (SCEs) were observed only in cultures treated with O,O-dimethyl O-[3-methyl-4-(methylthio)phenyl] phosphorothioate (Fenthion) at 40 and 80 ug/ml and S-[2-(ethylsulfinyl)ethyl]-O,O,-dimethyl phosphorothioate (oxydemeton-methyl) at 80 ug/ml. All compounds except O,O-diethyl O-[4-(methylsulfinyl)phenyl] phosphorothioate (Fensulfothion) and oxydemeton-methyl caused cell cycle delay in a dose-dependent fashion. O,O-dimethyl-S-[(4-oxo-1,2,3-benzotriazin-3(4H)-yl) methyl] phosphorodithioate (Azinphos-methyl: 40 and 80 ug/ml) did not induce SCEs, but w as highly toxic to V79 cells. Pesticides not producing SCEs are recommended as substitutes for those that do when distribution in the natural environment is contemplated. (9 Refs)

12. PROLIFERATION IN LOW CALCIUM MEDIUM AS A MARKER FOR MALIGNANCY: AN APPARENT EXCEPTION AMONG HUMAN CARCINOMA CELLS.

Swierenga SH, Auersperg N
Drug Toxicology Div., Health and Welfare Canada, Ottawa K1A OL2, Canada
Cancer Lett; 15(2):179-183 1982

Progression through the cell cycle of two cervical carcinoma lines (C4I and C-4II) having a reduced ability to form colonies in low-calcium medium was compared with that of a calcium-independent tumor cell line (C-33I) and a nontumorigenic cell line (T51B). T51B cells were unable to proliferate in low-calcium (0.02 milliM) medium, as shown by loss of colony-forming ability and reduced 3H-thymidine incorporation. C-33I cells, like other tumor cells, proliferated equally well in low- and high-calcium (1.8 milliM) medium. C4I cells, and to a lesser extent C-4II cells, formed few colonies in low-calcium medium; unlike normal cells, however, 3H-thymidine incorporation was unaffected by calcium deprivation. The number of dividing C-33I cells was not affected by calcium deprivation but was reduced in both normal T51B cells and in C-4 cells. Thus, the ability of C-4 cells to synthesize DNA, like other tumor cells, is unaffected by calcium deprivation, yet proliferation is arrested before metaphase and colony formation is reduced. Colony-forming assays should be followed by 3H-thymidine incorporation tests when calcium independence is used as a marker for malignancy. (11 Refs)

13. MEMBRANE TRANSPORT PROPERTIES DIFFER FOLLOWING RETURN OF SERUM-DEPRIVED VERSUS CA++-DEPRIVED HUMAN FIBROBLASTS TO A PROLIFERATIVE STATE.

Tupper JT, Ryals WT, Bodine PV
Dept. Biology, Syracuse Univ., Syracuse, NY, 13210
J Cell Physiol; 110(1):29-34 1982

The unidirectional influxes of Rb+, an analog for K+ transport, and of 3-O-methylglucose, cycloleucine, and alpha-aminoisobutyric acid were monitored following stimulation of quiescent WI38 human lung fibroblast cells by Ca++ or fetal bovine serum. Quiescence in the cells had been induced earlier by deprivation of one of the same two stimulants. The absence of Ca++ at the time of serum stimulation inhibited the increase in transport usually observed upon serum stimulation, but Ca++ stimulation did not stimulate transport in Ca++-deprived cells yet still caused cells to progress to S phase. Ca++ and serum inhibition of cell division apparently have different mechanisms. (34 Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

14. FLOW CYTOMETRIC ANALYSIS OF CELLULAR DNA IN HUMAN ACUTE NONLYMPHATIC LEUKEMIAS AND DYSMYELOPOIETIC SYNDROMES.

Maiolo AT, Fao P, Mozzana R, Chiorboli O, Ciani A, Maisto A, Starace G
Clinica Medica I, Univ. Milan, Milan, Italy
Cytometry; 2(4):265-267 1982

Cell cycle distribution in bone marrow specimens from untreated overt myeloid leukemias (ANLL; 16 patients) and dysmyelopoietic states (8 refractory anemias with excess blasts and 5 idiopathic refractory sideroblastic anemias) was studied. The DNA-flow cytometric patterns of leukemic cells in bone marrow aspirates and in vitro after culture on dialysis membranes were compared. No significant difference was found between the cell cycle distribution in ANLL and dysmyelopoietic states. Centrifugation can improve the percentage of immature proliferating cells in bone marrow; elutriation may be more effective. In ANLL, no relationship between the percentage of blast cells in the marrow and the size of the S phase compartment could be observed. Size of the S phase compartment was related to the in vitro growth of leukemic cells in liquid culture. When leukemic cells were cultured in vitro on dialysis membrane, the proliferation profile of the original sample was kept relatively constant. This in vitro technique allows myeloid cells to grow actively without any supply of exogenous stimulators, easy cell recovery for assessment of cell morphology and cytochemistry, and flow cytometry measurements. (12 Refs)

15. MITOSES AND MITOTIC ABERRATIONS IN HODGKIN'S DISEASE (MEETING ABSTRACT).

Friedman M
Radiation Therapy Department, Roswell Park Memorial Institute, 666 Elm Street, Buffalo, NY, 14263
UICC Conference on Clinical Oncology, October 28-31, 1981, Lausanne, Switzerland. International Union Against Cancer 131 pp., 1981.

Mitoses and mitotic aberrations found on cytologic specimens obtained from 343 patients with biopsy proven Hodgkin's Disease were recorded and analyzed. A total of 541 nodules and/or extranodal masses were punctured by using a 20 cc glass syringe and 18 gouge needle. Specimens were stained by the Wright-Giemsa Techhique. Mitotic phases of mononucleated cells (either reactive or tumoral) were frequently encountered. Most mitoses did not display gross aberrations detectable at the optical microscope. On fewer occasions, multipolar mitosis, lagging chromosomes in meta- and anaphase and polyploid cells were found. On the entire material, 23 binucleated cells and 31 cells with 3-8 nuclei, in synchronized prophases (41) or asynchronous mitoses (13) were seen. The close examination of some of the multinucleated cells in prophase suggests that nuclear random segmentation precedes the cell division. This study confirms experimental data that the Sternberg-Reed cell is capable of proliferation. The mitotic aberrations found in Hodgkin's Disease are similar to the atypical mitoses seen often in malignant tumors. (no Refs)

CELL CYCLE - SPECIFIC PHENOMENA

16. HISTONE PROTEINS IN HELA S3 CELLS ARE SYNTHESIZED IN A CELL CYCLE STAGE SPECIFIC MANNER.

Marashi F, Baumbach L, Rickles R, Sierra F, Stein JL, Stein GS
Dept. Biochemistry, Univ. Florida Coll. Medicine, Gainesville, FL, 32610
Science; 215(4533):683-685 1982

The synthesis of histone proteins in G1 and S phase HeLa S3 cells was examined by two-dimensional electrophoretic fractionation of nuclear and total cellular proteins. Newly synthesized histones were detected only in S phase cells. Histone messenger RNA sequences, as detected by hybridization with cloned human histone genes, were present in the cytoplasm of S phase but not G1 cells. (Author abstract) (27 Refs)

17. STIMULATION OF ALBUMIN SYNTHESIS IN MOUSE HEPATOMA CELLS BY BT2CAMP: CELL CYCLE SPECIFICITY.

Hamman HC, Ledford BE
Dept. Pharmacology, Univ. Virginia, Charlottesville, VA, 22908
Arch Biochem Biophys; 213(2):620-624 1982

Effects of cyclic AMP on mouse hepatoma cells (Hepa) proliferation and on albumin synthesis occurring during a specific phase of the cell cycle were studied. Relative rates of albumin synthesis were measured at various times after addition of dibutyryl cyclic AMP (Bt2cAMP) to the growth medium of synchronously growing cells. Results indicate that the relative rate of albumin synthesis increases after the cells enter the G1 phase of the cycle and that Bt2cAMP is required during the S phase. (15 Refs)

18. A TEMPERATURE-SENSITIVE MUTANT ISOLATED FROM MOUSE FM3A CELLS DEFECTIVE IN DNA REPLICATION AT A NON-PERMISSIVE TEMPERATURE.

Hyodo M, Suzuki K
Dept. Molecular Biology, Tokai Univ. Sch. Medicine, Bosecidai, Isehara-shi, Kanagawa-Ken 259-11, Japan
Exp Cell Res; 137(1):31-38 1982

Ts-131b, one of the temperature-sensitive (ts) mutants isolated from mouse FM3A cells, was found to be defective in DNA replication at a non-permissive temperature. After the cells were transfered to 39.5 C, the cell number increased by only 10% and the rate of incorporation of precursors into cellular DNA decreased rapidly. *Cell cycle analysis* by a flow cytometric method with the cells incubated at 39.5 C revealed that progression of the cells through the S phase was inhibited and most of the cells were arrested in the S phase. To study the defect in DNA replication of this ts-mutant at 39.5 C, DNA-fiber autoradiography was performed to measure the rate of DNA-chain elongation. The results showed that the rate of DNA-chain elongation was decreased at 6 hr after the temperature shift. However, since the decrease in the rate of DNA-chain elongation was not sufficient to account for the decrease in the rate of incorporation of the precursors, it was suggested that there was also a decrease in the rate of initiation of DNA replication at some of the replicon origins. (Author abstract) (31 Refs)

19. CELL CYCLE PATTERNS OF THYMIDYLATE SYNTHETASE AND 5,10-METHYLENETETRAHYDROFOLATE POLYGLUTAMATES IN CULTURED MOUSE HEPATOMA CELLS.

Priest DG, Doig MT, Ledford BE
Dept. Biochemistry, Medical University South Carolina, Charleston, SC, 29425
Experientia; 38(1):88-89 1982

The regulation of thymidylate synthetase activity was investigated throughout the first cell cycle after release from an isoleucine block in synchronous cultures of mouse hepatoma (Hepa) cells. Activity in cell extracts increased with the onset of S phase and the increased activity was attributed to a parallel increase in enzyme concentration as determined by titration with tritiated fluorodeoxyuridylate. The polyglutamate chain length of reduced folate cofactors, which could also influence thymidylate synthetase activity, was unchanged. (Author abstract) (24 Refs)

20. X-RAY INHIBITION OF DNA SYNTHESIS AT DISCRETE TIMES DURING S PHASE IN SYNCHRONOUS HUMAN DIPLOID FIBROBLASTS.

Kapp LN, Painter RB
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Radiat Res; 89(2):424-427 1982

The incorporation of thymidine into irradiated and unirradiated diploid fibroblasts at various times during S phase was investigated. Results indicated that most replicons initiate during relatively restricted times in S phase. Results support a model of diploid fibroblast S phase that consists of multiple initiations of large numbers of replicons during short, specific times. (12 Refs)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

21. CYTOTOXICITY OF L-CANAVANINE IN VITRO.

Naha PM
Dept. Cell Biology, Christie Hosp. and Holt Radium Inst., Paterson Labs., Manchester M20 9BX, England
Anticancer Res; 1(5):275-277 1981

Cytostatic cellular reactions caused by L-canavanine (CAN) were studied in BALB/c-3T3 cells and phytohemagglutinin-stimulated human lymphocytes. BALB/c-3T3 cells were exposed to L-arginine (ARG) or CAN at concentrations of 1 x 10(-4) M, 1 x 10(-5) M, or 5 x 10(-6) M for 48 hr. Human lymphocytes were exposed to CAN at 1 x 10(-4) M to 1 x 10(-6) M for 50 hr at 37 C, then mitotic indices, karyotypes, and sister chromatid exchanges were studied. Of BALB/c-3T3 cells exposed to CAN for 48 hr then placed in growth medium without CAN, 90% treated with up to 1 x 10(-4) M recovered to continue DNA synthesis within 24 hr. Compared with ARG-treated cells, high labeling indices were observed after withdrawal of CAN, probably due to partial synchrony caused by CAN-induced inhibition of DNA synthesis. At lower concentrations (1 x 10(-6) M), the lower labeling index suggested partial inhibition and poorer synchrony. Cells exposed to 1 x 10(-4) M CAN for 48 hr recovered to form colonies as efficiently as untreated controls. In the presence of CAN, however, there was total inhibition of colony-forming ability. In the presence of CAN, few phytohemagglutinin-stimulated lymphocytes proceeded with mitosis, while mitosis continued when CAN (1 x 10(-4) M) was withdrawn. No difference in chromosomal aberrations or sister chromatid exchanges were noted between CAN treated and control cultures. (17 Refs)

22. CYTOMORPHOLOGICAL CHANGES IN HUMAN TUMOR CELLS AFTER TREATMENT WITH HIGHLY POLAR COMPOUNDS.

Viadro MM, Tikhomirova EE, Timofeevskaia EA
Dept. Cytochemistry, Res. Inst. Biological Testing of Chemical Compounds, Moscow Oblast', USSR
Biull Eksp Biol Med; 91(11):586-588 1981

The effect of higly polar compounds dimethylsulfoxide (DMSO) and dimethylformamide (DMFA) on differentiation of tumor cells was studied in cells of human synovial sarcoma Sa-2 and osteogenic sarcoma Sa-4 growing in a monolayer. Incubation with DMSO or DMFA increased the number of round-shaped cells with basophilic cytoplasm and excentric localization of the nuclei. DMFA inhibited activity of acid phosphatase and alkaline phosphatase, while DMSO did not affect activity of cell enzymes. Both DMSO and DMFA increased the doubling time of tumor cells. These findings indicate that highly polar compounds induce the reversion of neoplastic differentiation. (15 Refs) (In RUS)

23. STUDY ON SYNCHRONIZATION THERAPY FOR NEUROBLASTOMA (MEETING ABSTRACT).

Sasaki F, Naito H, Une Y, Adachi T, Hata Y, Uchino J, Kasai Y
1st Department of Surgery, Hokkaido University School of Medicine, Sapporo, Japan
Proceedings of the Japanese Cancer Association, 40th Annual Meeting, October 1981, Sapporo, Japan. The Association 415 pp., 1981.

The synchronization therapy for neuroblastoma was undertaken in in vitro and in vivo experiments. Uncloned C-1300 cell line treated by 10(-4) ug/ml of Vincristine (VCR) showed G2+M phase accumulation. The treatment of CPM (cyclophosphamide), (1x10(-2) ug/ml) 24 hr after VCR had a more cytocidal effect than the treatment of CPM+VCR (simultaneous) or VCR following CPM. The most inhibition effect on the growth of the tumor transplanted into the back of mouse was recognized in the group with CPM treatment 12 hr after VCR administration. (no Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

24. CHARACTERIZATION OF RAPID RECOVERY FROM GAMMA-RAY DAMAGE IN PLATEAU-PHASE HUMAN DIPLOID FIBROBLASTS.

Malcolm AW, Tomkinson KN, Little JB
(c/o Little) Lab. Radiobiology, Harvard Univ., Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Radiat Res; 89(2):274-282 1982

The rapid recovery process in normal human diploid fibroblasts exposed to 50 rad/sec gamma rays at 4, 25, and 37 C was investigated. Normal human fibroblasts had the ability to recover partially from radiation damage very quickly at 25 or 37 C, and a significant proportion of all recovery was found to take place in the first minutes following exposure. Differences were dependent on both temperature and cell density. Faster recovery in denser cultures suggests an effect of cell-to-cell contact and cell cycle distribution. (21 Refs)

25. RESISTANCE OF A CULTURED FISH CELL LINE (CAF-MM1) TO GAMMA IRRADIATION.

Mitani H, Etoh H, Egami N
Zoological Inst., Tokyo Univ., Tokyo 113, Japan
Radiat Res; 89(2):334-347 1982

CAF-MM1 cells derived from the fin of the goldfish were studied to determine their resistance to gamma irradiation at 26 C. Values of D0 and Dq were 325 rad and 975 rad, respectively, indicating very low sensitivity in the presence of O2. After irradiation, the number of mitotic figures in the population decreased within 1 hr. Duration of G2 arrest was shorter than that observed in mammals. (27 Refs)

26. ALPHA-IRRADIATION-INDUCED G2 DELAY: A PERIOD OF CELL RECOVERY.

Lucke-Huhle C
Kernforschungszentrum Karlsruhe, Institut fur Genetik und fur Toxikologie von Spaltstoffen, Postfache 3640, D 7500 Karlsruhe 1, W. Germany
Radiat Res; 89(2):298-308 1982

Alpha particles with a linear energy transfer of about 110 keV/micrometer were very effective in causing G2 delay in exponentially growing Chinese hamster V79 cells. In contrast to the situation following x-ray or Cobalt 60 gamma irradiation, where even nonsurviving cells can proceed through several mitoses, the damage caused by alpha irradiation at doses higher than 0.5 Gy prevented mitosis in increasing fractions of irradiated cells in a dose dependent manner. It is concluded that the repair process inhibited by caffeine is essential for survival after alpha irradiation, and occurs in G2. (41 Refs)

OTHER RELATED STUDIES

27. THE TIME NEEDED FOR NORMALIZATION OF HAIRLESS MOUSE EPIDERMIS AFTER TREATMENT WITH TWICE WEEKLY TOPICAL SKIN APPLICATIONS OF 10 NMOL 12-O-TETRADECANOYLPHORBOL-13-ACETATE IN ACETONE, OR ACETONE ALONE, FOR 18 WEEKS. A MORPHOLOGIC AND CELL KINETIC STUDY.

Iversen OH, Paulsen JE, Schjolberg A
Inst. Pathology, Univ. Oslo, Rikshospitalet, Oslo 1, Norway
Carcinogenesis; 2(12):1353-1358 1981

In order to find the time needed for normalization of the mouse epidermis after an 18 wk-course of treatment according to the two-stage carcinogenesis protocol, hairless mice were treated with 10 nmol 12-O-tetradecanoylphorbol-13-acetate in 100 ul reagent grade acetone twice weekly for 18 wk. A control group was treated similarly with 100 ul reagent grade acetone alone. Groups of four animals were killed each wk for 10 wk thereafter, and morphologic and cell kinetic studies performed. To assess hyperplasia, the number of basal and suprabasal cells per unit length of epidermis was counted. The mitotic rate was determined by a stathmokinetic method using Colcemid for arrest of mitoses. DNA synthesis was measured by determining the labeling index and the DNA-specific activity after injection of [3H]thymidine. F low cytometric measurements were performed to find the fraction of cells in the various cell cycle phases at each observation point. Treatment with acetone alone led to a moderate hyperplasia and a slight increase in the mitotic rate, which persisted during the 10 wk of subsequent observation. Treatment with TPA led to a considerable hyperplasia which first increased for 3 wk and then decreased, and was still significant 10 wk after termination of treatment. The line of best fit through the values indicated that a time of about 20 wk may be needed before normal epidermal thickness is reestablished. TPA treatment also led to a pronounced increase in the labeling index and a high mitotic rate. These variables became almost normal after approx 8-10 wk, but one cannot know whether one or more new waves of proliferation take place more than 10 wk after termination of TPA treatment. If a proper 'inverse' experiment according to the two-stage theory of carcinogenesis should be performed, one had to wait at least 20 wk after termination of promotion before the initiating dose of carcinogen should be applied. The possibility of increased acquired resistance to carcinogens during promotion is also discussed. (Author abstract) (10 Refs)

28. STARVATION OF ARGININE AND GLUTAMINE SENSITIZES HUMAN DIPLOID CELLS TO THE TRANSFORMING EFFECTS OF N-ACETOXY-2-ACETYL-AMINOFLUORENE.

Zimmerman RJ, Little JB
(c/o Little) Lab. Radiobiology, Harvard Sch. Public Health, 665 Huntington Ave., Boston, MA, 02115
Carcinogenesis; 2(12):1303-1310 1981

We have examined the influence of the method of synchronization on the transformation of normal human diploid fibroblasts treated in mid-S phase with N-acetylaminofluorene (N-Ac-AAF), and on the subsequent kinetics of the removal of carcinogen damage. At early times posttreatment, the transformation frequency in cultures synchronized by a 24 hr starvation for arginine and glutamine was enhanced over that of cultures synchronized by release from confluence. In cells synchronized by either method, transformation was enhanced at all times when the cells were incubated after treatment in medium containing high concentrations of nonessential amino acids, vitamins and serum. Synchronized cells treated with 3 uM [3H]N-Ac-AAF in mid-S removed significantly less DNA damage than cultures treated and held under confluent, noncycling conditions. Cells synchronized by amino acid starvation removed less damage than cells synchronized by release from confluence. S-phase treatment of synchronized cells resulted in a dose-dependent delay of DNA replication. The early, rapid phase of repair was temporally correlated with the delay in S-phase progression. We conclude from these data that synchrony achieved by amino acid starvation renders human cells more sensitive to N-Ac-AAF-induced transformation in vitro than does that achieved by release from density-inhibiti on of growth. The S-phase treated, cycling cells lost only about 10% of their initial carcinogen damage before reinitiation of treatment-delayed bulk DNA synthesis. These results support the hypothesis that the persistence of carcinogen damage in replicating DNA may be an important factor in cell transformation. (Author abstract) (46 Refs)

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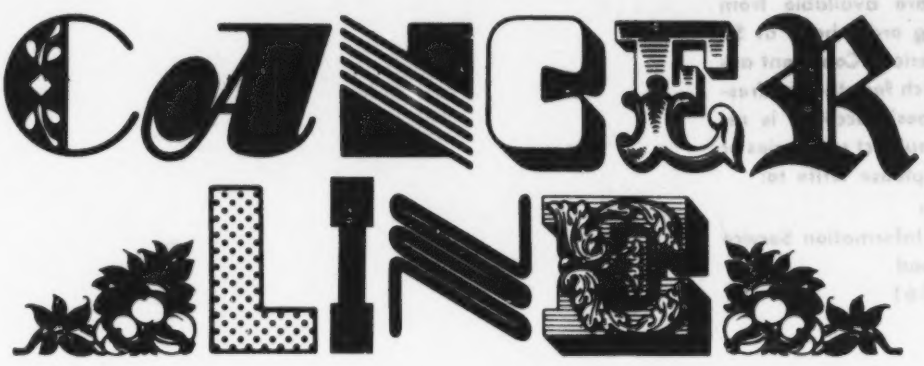

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KINETIC METHODS AND MODELS

1. A METHOD FOR THE MEASUREMENT OF VARIABILITY IN CELL LIFETIMES.

Cowan R, Culpin D
CSIRO Div. Mathematics and Statistics, P. O. Box 218, Lindfield, New South Wales 2070, Australia
Math Biosci; 54(3/4):249-263 1981

The numbers of S-phases encountered by a cell during a known period of time were studied in chick embryo retinal

HE 20.3173/2:

cells continuously labeled with 5-bromo-2'-deoxyuridine (BUdR) and selectively stained. The BUdR-labeled cells were examined during metaphase or late prophase. In cells which had passed through 0-1 S-phases after BUrD exposure, both members of a given chromatid pair were darkly stained. The proportions of stained chromosomes declined after each successive cell division. This BUdR labeling method is a considerable refinement on the fraction-labeled mitosis technique, which determines only whether or not a cell has encountered an S-phase. (14 Refs)

2. DIFFUSION CHAMBER (DC) CULTURING OF HAEMOPOIETIC CELLS: A RELIABLE ASSAY SYSTEM FOR REGULATORS OF PROLIFERATION?

Benestad HB, Toogood EO
Inst. Physiology, Karl Johansgt. 47, Oslo 1, Norway
Exp Hematol; 10(2):161-171 1982

If ip DC culturing of hemopoietic cells shall serve as a reliable assay for systemic and/or local peritoneal regulators of proliferation, cell growth must not be restricted by the diffusion capacity through the chamber membranes. Diffusion was assessed by measuring uptake in DC or 51Cr-EDTA of 3H-thymidine, given intravenously to mouse hosts or to chambers incubated in vitro. Fractional incorporation of 3H-thymidine, numbers of mouse spleen colony-forming stem cells, agar colony-forming progenitors (of granulocytes and macrophages), and total cell numbers were taken to reflect cell growth. Changing the diffusion capacity did not not lead to marked changes in cell growth; and vice versa, culturing cells under host or chamber conditions that increased cell growth was not associated with an appreciably increased diffusion capacity. Diffusion was increased by replacing Acropor with Millipore DC or by repeatedly cleaning the DC during the culture period. Cell growth was increased by using irradiated rather than normal host mice, and Nuclepore rather than Milipore DC in irradiated mice. Increasing the oxygen delivery to the cultured cells by using polycythemic and hyperoxic hosts did not enhance cell growth either. (Author abstract) (20 Refs)

3. EXPONENTIAL GROWTH OF CELL COUNT. I. INDEPENDENCE OF A FRACTION OF PROLIFERATING CELLS IN DIFFERENT STAGES OF CELL CYCLE FROM THE VARIABILITY OF STAGE DURATION.

Goshchin VA
Computer Dept., Central Res. Roentgeno-Radiological Inst., Leningrad, USSR
Tsitologiia; 23(12):1428-1436 1981

Mathematical model of tumor cell kinetics is described. Assuming the exponential growth of the cell number and zero cell loss, the fraction of proliferating cells in each stage of mitotic cycle was shown to be independent from the duration of this stage. Proliferating pool, av duration of mitosis, and cell doubling time can be estimated from indices of the stages S and M, av duration of G2 0.5M stage, S stage, and M cycle. (12 Refs) (In RUS)

4. A MODEL FOR THE EFFECT OF EXCISION REPAIR ON THE SURVIVAL OF HUMAN CELLS EXPOSED TO CHEMICAL CARCINOGENS.

Miller JH, Heflich RH
Pacific Northwest Lab., Richland, WA, 99352
Chem Biol Interact; 39(1):45-55 1982

A model is presented which correlates the survival of normal human fibroblasts (NF) after exposure to N-acetoxy-2-acetylaminofluorene (N-AcO-AAF) with the rate of excision of carcinogen residues bound to DNA. Measurements of the rate of excision of carcinogen residues suggest that this is a first-order process with 37% of the adducts remaining after about 70 hr. From this information and the dose-response relationship for survival of NF and repair deficient cells we can determine the mean number of adducts required to produce a potentially lethal lesion and the effective time available for repair. When these adjustable parameters have been determined, we can use the model to predict the rate of excision in partially repair-deficient cells and the effect of extending the repair period by arresting cell growth after treatment. Survival studies in which cells were held at confluence for varying amounts of time between treatment and replating at low density show good agreement with the predictions of the model. (Author abstract) (14 Refs)

GROWTH CHARACTERISTICS OF NORMAL CELLS AND TUMOR CELLS IN VIVO

5. A THEORETICAL CONSIDERATION OF SOME BIOLOGICAL PARAMETERS INVOLVED IN CELL KINETIC INVESTIGATIONS OF ORAL LEUKOPLAKIA AND ABNORMAL STATES IN STRATIFIED SQUAMOUS EPITHELIUM.

Hume WJ
Paterson Lab., Christie Hosp. and Holt Radium Inst., Manchester M20 9BX, England
J Oral Pathol; 10(6):375-385 1981

Common biological parameters which should be considered when studying cell kinetic data of normal and pathological epithelia are outlined. These include heterogeneity, growth fraction, age distribution, cell synchronization, phase-duration estimation, steady-state conditions, and error limits. An altered mitotic index in such abnormal states as leukoplakia need not indicate an abnormality of cell proliferation. (46 Refs)

GROWTH CHARACTERISTICS OF TISSUE CULTURES AND DERIVED CELL LINES

6. MONOCLONAL ANTIBODY TO TRANSFERRIN RECEPTOR BLOCKS TRANSFERRIN BINDING AND INHIBITS HUMAN TUMOR CELL GROWTH IN VITRO.

Trowbridge IS, Lopez F
Dept. Cancer Biology, Salk Inst. Biological Studies, P. O. Box 85800, San Diego, CA, 92138
Proc Natl Acad Sci USA; 79(4,part1):1175-1179 1982

A murine hybridoma has been obtained that produces a monoclonal antibody against the human transferrin receptor. In contrast to previously characterized monoclonal antibodies that recognize the transferrin receptor, this antibody, designated 42/6, blocks the binding of transferrin to its receptor and inhibits the growth of the human T leukemic cell line, CCRF-CEM, in vitro. Inhibition of cell growth was dose dependent, and as little as 2.5 ug of purified antibody per ml had a detectable effect, even though transferrin was present in the tissue culture medium in large molar excess. Cells grown in the p resence of antibody for 7 days accumulated in S phase of the cell cycle.

The addition of iron to antibody-treated cultures in the form of ferric complexes or ferrous sulfate did not overcome the growth inhibitory effects of the anti-transferrin-receptor antibodies. This result suggests that either transferrin is the only means by which CCRF-CEM leukemic cells can be provided with sufficient iron in vitro or that other factors in addition to iron starvation are involved in the antibody-mediated growth inhibition. The inhibition of cell growth by 42/6 monoclonal antibody suggests that monoclonal antibodies against proliferation-associated cell surface antigens, such as the transferrin receptor, may be useful pharmacological reagents to modify cell growth in vitro. (Author abstract) (46 Refs)

7. REARRANGEMENTS OF DNA-PROTEIN INTERACTIONS IN ANIMAL CELLS COUPLED WITH CELLULAR GROWTH-QUIESCENCE TRANSITIONS.

Lichtenstein AV, Sjakste N, Zaboykin MM, Shapot VS
All-Union Oncological Scientific Center, Moscow 115478, USSR
Nucleic Acids Res; 10(3):1127-1145 1982

Overall DNA-protein interactions in animal cells undergo drastic changes coupled with cellular transitions from quiescence to growth and reversely as revealed by nucleoprotein-Celite chromatography. DNA of chromatin was found to exist in one of the two sharply distinct alternative forms, namely, either tightly or weakly bound to protein moiety. These forms are specific for cycling and quiescent cells, respectively. The tight DNA-protein interactions characterize all cycling cells independent of the cell cycle phase. Transition of DNA of cycling cells from one form to another was observed as a result of treatment of isolated nuclei with DNase I. (Author abstract) (18 Refs)

8. STRIPPING OF EXTERNAL CELL-ASSOCIATED FIBRONECTIN FROM MITOTIC FIBROBLASTS.

Iwashita S, Yahara I
Tokyo Metropolital Inst. Medical Science, Honkomagome 3-18, Bunkyo-ku, Tokyo 113, Japan
Cell Struct Funct; 6(4):313-327 1981

The timing of release of fibronectin (FN) according to cell cycle phase was studied in the C3H2K mouse fibroblastic cell line using trypsinization to stimulate arrested cells and hydroxyurea (HU) to prevent progression of the cell cycle in trypsinized cells. HU-treated and untreated cells showed no significant difference in FN release, suggesting that FN release into the medium is not cell-cycle dependent. Immunofluorescence showed that mitotic cells tend to become round and leave FN networks on the surface of the substratum surrounding the point where they were attached. (26 Refs)

9. INFLUENCE ON THE CELL CYCLE PROGRESSION OF HELA CELLS BY C PARVUM ACTIVATED MACROPHAGES.

Haskill S
Dept. Obstetrics and Gynecology, Univ. North Carolina, 620 F.L.O.B. Building, Chapel Hill, NC, 27514
J Reticuloendothel Soc; 31(1):85-98 1982

Dual parameter flow cytometry has been utilized to study the effect of C parvum activated mouse macrophages on HeLa cells. Identification of tumor cells in the presence of macrophages was facilitated by their distinct fluorescence with propidium iodide and fluorescein conjugated antiplacental alkaline phosphatase (PAP). The two parameters determined simultaneously provided an accurate quantitative assessment of HeLa cells. Dose response relationships between normal (NMphi) and C parvum (CpMphi) activated macrophages simultaneously assayed by tritiated thymidine (3HTdR) incorporation or direct assessment of the absolute number of tumor cells per well indicated that flow cytometry was a sensitive method of determining growth inhibition and cytotoxicity. Following incubation with CpMphi, the majority of HeLa cells appeared to survive in the G0G1 phase of the cell cycle, irregardless of whether or not both growth inhibition and cytoxicity had occurred. HeLa cells isolated in the G0G1 phase by unit gravity sedimentation were readily destroyed by CpMphi. Surviving tumor cells did not enter into S phase. The large increase in PAP on these cells indicated their viability in this growth arrested state. Target cells predominantly in late S and G2 phase were also sensitive to the cytolytic mechanism of CpMphi. However, the surviving cells were apparently not growth inhibited until they had passed through mitosis and entered the G1-S interphase. Prelabeled HeLa cells separated into different proportions of the various cell cycle phases were equally sensitive to activated macrophages. The results indicate that while cytotoxicity appears to occur throughout the cell cycle, growth inhibition is more specific and is a result of a block at or near the G1-S interphase. (Author abstract) (18 Refs)

10. CELL-CYCLE CHARACTERISTICS OF UNDIFFERENTIATED AND DIFFERENTIATING EMBRYONAL CARCINOMA CELLS.

Rosenstraus MJ, Sundell CL, Liskay RM
Dept. Biological Sciences, Douglass Coll., Rutgers Univ., New Brunswick, NJ, 08903
Dev Biol; 89(2):516-520 1982

Subclone OTF9-63 of the F9 mouse embryonal carcinoma (EC) cell line and the PSA-1 EC cell line were studied by (3H)thymidine pulse-labeling to measure cell cycle parameters and to determine which compartments of the cell cycle are altered during differentiation. Control OTF9-63 cultures grew with a generation time of 12 hr and the following phase lengths: G1 less than 0.5 hr, S approx 10 hr, and G2 M approx 2 hr. Cultures treated with 0.1 uM retinoic acid for induction of differentiation exhibited the following av parameters: generation time 16.8 hr, G1 2.3 hr, S 12.5 hr, and G2 2.0 hr. Slowing the growth rate by reducing culture temperature to 33 C did not induce endodermal differentiation in this line. Similar cell cycle analysis of PSA-1 cells yielded a generation time of approx 12 hr for undifferentiated monol ayers (G1 less than 0.5 hr, S 9-9.5 hr, G2 M, 2.5 hr) and a generation time of approx 20 hr for naturally-differentiating aggregation cultures (G1 1.9 hr, S 16.3 hr, G2 M 2.2 hr). The data demonstrate that both G1 and S increase in EC cell populations during induced differentiation, but the cell-cycle lengths of the phases in individual cells actually differentiating can only be determined if a marker for differentiating cells is used. (26 Refs)

11. GROWTH AND DIFFERENTIATED PROPERTIES OF A KIDNEY EPITHELIAL CELL LINE (MDCK).

Saier MH
Dept. Biology, John Muir Coll., Univ. California San Diego, La Jolla, CA, 92093
Am J Physiol; 240(3):C106-C109 1981

Physiologic, biochemical, genetic, and electron-microscopic findings in regulation of Madin-Darby canine kidney (MDCK) epithelial cell function are reviewed. Growth regulatory properties, growth in hormonally defined serum-free medium, isolation and properties of virally and chemically transformed variants of MDCK cells, differentiated properties of MDCK cells

in vitro, and sodium ion transport systems in MDCK cells are discussed. (18 Refs)

KINETICS OF THE HEMATOPOIETIC AND IMMUNE SYSTEMS

12. ANALYSIS OF THE EFFECT OF HYDROXYUREA ON STEM CELL (CFU-S) KINETICS.

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Dept. Pathophysiology, Faculty Medicine, Charles Univ., U nemocnice 5, 128 53 Praha 2, Czechoslovakia
Cell Tissue Kinet; 15(1):39-47 1982

Hydroxyurea induces profound changes in the pluripotential hemopoietic stem cell (CFU-s) kinetics. The main feature of these changes is a synchronous entry of resting G0 CFU-s into the cell cycle. The analysis of the passage of the CFU-s cohort through the cell cycle has been largely based on the examination of the fraction of CFU-s which synthesize DNA in the S phase of the cell cycle. This analysis has, however, been hampered by the fact that both the sensitivity of the S phase CFU-s to hydroxyurea and their sensitivity in the [3H]thymidine suicide technique vary as the cells pass through the S phase. Methods which overcome these difficulties have been used in the experiments presented in this paper. It was demonstrated that hydroxyurea kills only about 80% of the S phase CFU-s. The sensitivity to hydroxyurea gradually decreases as the cells approach the middle part of the S phase and increases again as the cells enter the late portions of the S phase. The degree of CFU-s synchrony at the point of entry into and exit from, the S phase has been established. Mathematical analysis of the available data suggests that CFU-s pass through the S phase with a mean transit time of 4.79 hr (standard deviation, 1.45 hr). Hydroxyurea, administered in vivo, blocks CFU-s in the late G1 phase. The duration of this G1-S block, induced by a dose of 1,000 mg of hydroxyurea per kg body wt, is approx 2 hr. The CFU-s in the middle of the S phase, which survive h ydroxyurea administration, are also blocked in their passage through the S phase. These cells, however, seem to finish the S phase with a delay of approx 2 hr. (Author abstract) (13 Refs)

13. RETARDATION AND PROMOTION OF GROWTH OF SPONTANEOUSLY APPEARING TUMORS USING IMMUNE LYMPHOCYTES PREVIOUSLY EXPOSED TO EMBRYONIC ANTIGENS.

Gorczynski RM, MacRae S
Ontario Cancer Inst., Toronto M4X 1K9, Ontario, Canada
Cancer Res; 42(3):784-790 1982

Spleen lymphocytes taken from mice at various stages of pregnancy or growth of sc syngeneic tumor implants have been examined for their ability to cause cytolysis of embryo fibroblasts in culture or to affect the growth of the transplanted tumor cells in vivo. Activity of different lymphoid populations in affecting tumor growth in vivo was correlated with activity in vitro, whether cytolysis (growth inhibition) or blocking of cytolysis (growth promotion) was considered. The evidence favors an important role for lymphoid responses to embryo-associated antigens in the control of spontaneous tumor growth, although one cannot yet rule out a crucial role for the host milieu rather than, or in addition to, host cellular elements being the important feature of this control process. (Author abstract) (29 Refs)

14. ACTIVATION OF SUPPRESSOR T CELLS BY AUTOLOGOUS LYMPHOBLASTOID CELLS: A MECHANISM FOR FEEDBACK REGULATION OF IMMUNOGLOBULIN SYNTHESIS.

James SP, Yenokida GG, Graeff AS, Strober W
Immunophysiology Section, Metabolism Branch, NCI, NIH, Bethesda, MD, 20205
J Immunol; 128(3):1149-1154 1982

In this study, the regulatory potential of T cells activated as a result of exposure to autologous lymphoblastoid cells was examined. In initial studies it was observed that the proliferative response of T cells induced by exposure to mitogen-transformed or Epstein Barr virus (EBV)-transformed autologous lymphoblastoid cells was greater than the proliferative response of T cells induced by exposure to unstimulated autologous B cells. Such activated T cells profoundly suppressed pokeweed mitogen (PWM)-stimulated immunoglobulin synthesis by autologous indicator cells, but compared to fresh T cells or cultured T cells, these activated cells had a diminished capacity to provide help for PWM-stimulated immunoglobulin synthesis. In additional studies it was found that (1) both PWM-transformed B cells and EBV-transformed B cells were able to activate suppressor T cells, suggesting that the mechanism of activation is independent of the agent used to transform the lymphoid cells; (2) T cells cultured with PWM-induced lymphoblastoid cells did not suppress immunoglobulin synthesis when added to PWM-stimulated cells after 3 days of culture, indicating that suppression was not due to killing of immunoglobulin-secreting cells; (3) mitogen-induced lymphoblastoid cells acquired maximal ability to activate suppre ssor T cells after 3 days of culture with the mitogen, indicating that lymphoid cells had to undergo mitogen-induced changes to activate suppressor T cells. These results are compatible with the concept that when B cells are activated to differentiate into immunoglobulin-secreting cells, they express new determinants that are capable of activating suppressor T cells, which can then act to inhibit further B cell differentiation. (Author abstract) (26 Refs)

15. INDUCTION OF DIFFERENTIATION OF HUMAN PROMYELOCYTIC LEUKEMIA (HL-60) CELLS BY TELEOCIDIN AND PHORBOL-12-MYRISTATE-13-ACETATE.

Huberman E, Braslawsky GR, Callaham M, Fugiki H
Biology Div., Oak Ridge Natl. Lab., Oak Ridge, TN, 37830
Carcinogenesis; 3(1):111-114 1982

Human promyelocytic leukemia cells (HL-60) were induced to differentiate into macrophage-like cells in a dose-dependent manner by the tumor promoters phorbol-12-myristate-13-acetate and teleocidin, a non-phorbol ester promoter. An HL-60 cell variant, designated as R-59, which is resistant to differentiation induction by phorbol-12-myristate-13-acetate was also resistant to differentiation induction by teleocidin. Differentiation was determined by increases in the percent of morphologically mature cells and in lysozyme and nonspecific esterase activities. Both compounds inhibited the growth of HL-60 cells by blocking them from entering the synthesis phase of the cell cycle with an accumulation of cells after 48 hr in G1 phase. No such effects were observed in the R-59 cells. They were, however, as susceptible as the parent HL-60 cells, to inducers which are not considered to be tumor promoters such as dimethylsulfoxide and retinoic acid. However, these inducers cause the HL-60 and R-59 cells to differentiate into granulocyte-like cells. These results indicate that teleocidin produces

in both the HL-60 and R-59 cells effects which are similar to those caused by phorbol-12-myristate-13-acetate. The possibility that agents producing such effects in these two cell types may represent potential tumor promoters is discussed. (Author abstract) (28 Refs)

16. PROLIFERATIVE CAPACITY OF MURINE HEMATOPOIETIC STEM CELLS IN VITRO.

Reincke U, Hannon EC, Rosenblatt M, Hellman S
Dept. Radiation Therapy, Harvard Medical Sch., Boston, MA, 02115
Science; 215(4540):1619-1622 1982

Large numbers of granulocytes can be collected repeatedly from the supernatant medium of long-term cultures of mouse bone marrow cells. A constant relationship was found between the number of adherent hematopoietic stem cells and the lifetime cell production per culture. The data indicate that there is a limit to the proliferative capacity of normal and of irradiated stem cells. A similar limitation was found in the production of marked granulocytes from clonal cultures of 'beige' C57(bg/bgJ) st em cells placed in limiting dilutions into stromal culture layers. (Author abstract) (38 Refs)

17. VELOCITY SEDIMENTATION PROFILES OF NORMAL AND REGENERATING PRIMITIVE ERYTHROID BURST-FORMING UNITS: RELATION TO PHASE OF CELL CYCLE AND GROWTH IN VITRO.

Koury MJ, Krantz SB
Div. Hematology, Vanderbilt Univ. Sch. Medicine, Room A-5102, Nashville, TN, 37232
Cell Tissue Kinet; 15(1):59-67 1982

The primitive burst-forming unit-erythroid (BFU-e) derived from normal and regenerating murine bone marrow was examined by velocity sedimentation at unit gravity. An increase in the modal sedimentation velocity and the percentage of rapidly sedimenting BFU-e was found in regenerating marrow as compared to normal marrow. Neither hypertransfusion-induced plethora nor administration of erythropoietin (Ep) during regeneration altered the changes from normal in the velocity sedimentation profile observed during regeneration. Separated marrow cells were pooled as rapidly sedimenting and slowly sedimenting and then examined for percentage of BFU-e in DNA synthesis and growth response in vitro to increasing concentrations of a partially purified Ep preparation. The percentage of BFU-e in DNA synthesis as determined by tritiated thymidine killing does not correspond to the BFU-e growth response to Ep in vitro. No difference in growth was noted between BFU-e from rapidly and slowly sedimenting normal marrow cells despite an increased percentage in DNA synthesis of normal BFU-e which sedimented rapidly. No significant difference in the percentage of BFU-e in DNA synthesis was found between the rapidly and slowly sedimenting subpopulations of regenerating BFU-e, but the latter had a reduced growth response to low concentrations of Ep. (Author abstract) (23 Refs)

CELL CYCLE - SPECIFIC PHENOMENA

18. QUANTITATIVE ANALYSIS OF EHRLICH TUMOUR CELL NUCLEOLI DURING INTERPHASE.

Lepoint A, Goessens G
Inst. Histology, Univ. Liege, B-4020 Liege, Belgium
Exp Cell Res; 137(2):456-459 1982

Nuclear and nucleolar growth throughout interphase has been analyzed by stereological methods. The nuclear volume and the volumes of the different nucleolar components have been determined in Ehrlich tumor cells selected at various stages of the cell cycle. These quantitative electron microscopic investigations demonstrate that the nuclear and nucleolar volumes are twice as large in G2 as in G1 cells. In addition, all the nucleolar constituents participate in this latter process. (Author abstract) (21 Refs)

19. ANALYSIS OF HISTONE GENE EXPRESSION DURING THE CELL CYCLE IN HELA CELLS BY USING CLONED HUMAN HISTONE GENES.

Rickles R, Marashi F, Sierra F, Clark S, Wells J, Stein J, Stein G
Dept. Immunology and Medical Microbiology, Univ. Florida, Gainesville, FL, 32610
Proc Natl Acad Sci USA; 79(3):749-753 1982

Although it is generally agreed that histone protein synthesis is restricted to the S phase of the cell cycle - and therefore parallels DNA replication - both transcriptional and posttranscriptional levels of control have been invoked. Using blot hybridization with several cloned genomic human histone sequences representing different histone gene clusters as probes, we have assessed the steady-state level of histone RNAs in the nucleus and cytoplasm of G1 and S phase HeLa S3 cells. The representation of histone mRNA sequences of G1 compared with S phase cells was less than 1% in the cytoplasm and approx 1% in the nucleus. These data are consistent with transcriptional control, but we cannot completely dismiss the possibility that regulation of histone gene expression is, to some extent, mediated posttranscriptionally. If histone gene transcription does occur in G1, the RNAs must either be rapidly degraded or be transcribed to a limited extent compared with S phase. An unexpected result was obtained when a blot of cytoplasmic RNA from G1 and S phase cells was hybridized with lambdaHHG 41 DNA (containing H3 and H4 human genomic histone sequences). Although hybridization with histone mRNAs was observed for RNAs from S phase but not from G1 cells, hybridization with a nonhistone RNA of approx 330 nucleotides present predominantly in G1 was also observed. (Author abstract) (29 Refs)

20. ALKALI-LABILE LESION AND URACIL-DNA-GLYCOSYLASE-SENSITIVE SITE REMOVAL AFTER BRDURD AND UVB TREATMENT OF CHINESE HAMSTER CELLS.

Hagan MP, Matsushita T, Bonura T, Shotola A
Dept. Experimental Hematology, Armed Forces Radiobiology Res. Inst., Bethesda, MD, 20014
Photochem Photobiol; 35(3):371-377 1982

A marked cell-cycle dependency for the recovery of cells after BrdUrd UVB treatment has led us to look for similar characteristics in the molecular events associated with DNA repair. Such characteristics are reported here for the repair of alkali-labile lesions. When asynchronously growing cells were uniformly substituted with BrdUrd (a condition that results in

the greatest cell killing), the repair kinetics followed a simple exponential response with a half-time of approx 17 min. However, when lesions were restricted to 3-5% of the genome and the repair observed in the mid-S phase (a condition associated with sublethal damage repair), the DNA repair kinetics were complex. The rejoining of the DNA was biphasic with greater than 90% of the lesion with a half-time of less than 6-7 min. Uracil removal followed similar kinetics. Caffeine, a potent inhibitor of cell survival after BrdUrd/UVB treatment, had no measurable effect on either uracil removal or alkali-labile lesion repair. (Author abstract) (27 Refs)

EFFECTS OF CHEMICAL AGENTS AND DRUGS ON MITOTIC ACTIVITY

21. THE STRUCTURE OF METHYLATED XANTHINES IN RELATION TO THEIR EFFECTS ON DNA SYNTHE SIS AND CELL LETHALITY IN NITROGEN MUSTARD-TREATED CELLS.

Murnane JP, Byfield JE, Chen CT, Wang CH
Lab. Radiobiology, Univ. California, San Francisco, CA, 94143
Biophys J; 35(3):665-676 1981

The relationship between structural differences in caffeine side chains and differences in the effects of substituted xanthines on cellular processes was studied using the human colon carcinoma cell line HT-29. The effects of caffeine, theobromine, theophylline, paraxanthine, 3-isobutyl-1-methylxanthine, pentoxyphylline, 1-n-butyl-3,7-dimethyl xanthine, 1-n-propyl-3,7-dimethyl xanthine, with or without nitrogen mustard, on HT-29 cells in colony formation assays and on (3H)thymidine incorporation were analyzed in relation to side chain differences. The compounds varied greatly in their effects on HT-29 cells in both tests, with or without HN2. Alkylated xanthines in general produced elevations in DNA synthesis in HN2-damaged DNA at concentrations corresponding to those required for synergistic lethality. Such a result is consistent with the hypothesis that inhibition of replicon initiation in response to HN2, a survival mechanism to prevent expression of damaged genes, is reversed by the xanthines. Enhancement of HN2 lethality is less at toxic levels of xanthines, probably because toxic concentrations prevent cells from passing through the S phase. Lethality of xanthines alone in undamaged cells is apparently related to an immediate inhibition of incorporation of exogenous thymidine. (38 Refs)

22. ACCUMULATION OF S PHASE POPULATIONS OF FM3A CELLS GROWING IN THE MOUSE DUE TO ADMINISTRATION OF 5-FLUORO-2'-DEOXYURIDINE.

Hanaoka F, Nagata K, Watanabe Y, Enomoto T, Yamada M
Dept. Physiological Chemistry, Faculty Pharmaceutical Sciences, Univ. Tokyo, Hongo, Bunkyo-ku, Tokyo 113, Japan
Cell Struct Funct; 6(4):357-365 1981

Procedures and results of administration of 5-fluoro-2'-deoxyuridine (FudR) to mouse FM3A cells growing in the mouse peritoneal cavity are described. A single administration of 100 ug FUdR caused the accumulation of 70-80% of FM3A cells in the S phase; indirect evidence suggests that most of the cells were at the G1/S boundary. The cytoplasmic fraction of mouse FM3A cells contained a very high level of the P-1 fraction of DNA polymerase alpha, and the DNA polymerase alpha in nuclear extract from FUdR-treated cells was about 3x as active as that from the randomly-growing cells. (14 Refs)

23. ELEVATED LEVEL OF ENZYMATIC DNA METHYLATION IN CELLS TREATED WITH 1-BETA-D-ARABINOFURANOSYLCYTOSINE.

Boehm TL, Drahovsky D
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Cancer Res; 42(4):1537-1540 1982

When mouse P815 mastocytoma cells are cultured in the presence of 1-beta-D-arabi nofuranosylcytosine (ara-C), a dose-dependent inhibition of cell proliferation and DNA synthesis can be observed. The DNA synthesized in the presence of ara-C is more highly enzymatically methylated than that of controls as measured by conversion of incorporated [14C]deoxycytidine-derived radioactivity into 5-methylcytosines. Analysis of DNAs by means of the bacterial restriction enzyme Hpall and its isoschizomer Mspl revealed an aberrant DNA methylation pattern after ara-C treatment. The hypermethylation of DNA persisted also in the cell cycle following the treatment in the absence of ara-C. No such changes in DNA methylation patterns following ara-C treatment were observed in P815/ara-C, a subclone of P815 cells resistant to ara-C. (Author abstract) (22 Refs)

24. A COMPARISON OF THE LETHAL AND KINETIC EFFECTS OF DOXORUBICIN AND 4'-EPI-DOXORUBICIN IN VITRO.

Hill BT, Whelan RD
Lab. Cellular Chemotherapy, Imperial Cancer Res. Fund, Lincoln's Inn Fields, London WC2A 3PX, England
Tumori; 68(1):29-37 1982

In vitro lethal and kinetic effects of 4'-epi-doxorubicin (EPI-DXR) have been established and compared with those of doxorubicin (14-hydroxy-daunorubicin, adriamycin, NSC-123127, DXR). Both drugs show comparable cytotoxicity against a range of murine and human cell lines. Cytotoxicity increased exponentially with drug concentration and with duration of exposure. EPI-DXR like DXR exerts maximal lethal effects during the late S and G2 phases of the cycle in synchronized NIL8 Syrian hamster cells. Flow microfluorimetric data and measurements of mitotic indices provide evidence of population arrest in G2 with both drugs. Responses of various drug-resistant L5178Y cell lines were similar for DXR and EPI-DXR: (i) DXR-resistant cells exhibit complete cross-resistance to EPI-DXR, (ii) vincristine-resistant cells are cross-resistant to DXR and EPI-DXR, and (iii) methotrexate-resistant and 5-fluorouracil-resistant cells show collateral sensitivity to both drugs. These studies emphasize the similarities of DXR and EPI-DXR. (Author abstract) (34 Refs)

25. NEW ANTITUMOR IMIDAZOLE DERIVATIVE, 5-CARBAMOYL-1H-IMIDAZOL-4-YL PIPERONYLATE, AS AN INHIBITOR OF PURINE SYNTHESIS AND ITS ACTIVATION BY ADENINE PHOSPHORIBOSYLTRANSFERASE.

Fukui M, Inaba M, Tsukagoshi S, Sakurai Y
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Cancer Res; 42(3):1098-1102 1982

The mechanism of action of 5-carbamoyl-1H-imidazol-4-yl piperonylate (SL-1250) which has a broad antitumor spectrum, was examined by in vitro cell culture and enzymatic studies. In the serum-containing culture medium, SL-1250 was rapidly deacylated to 4-carbamoylimidazolium 5-olate (SM-108). Thus,

SL-1250 might be acting on the cells in the form of SM-108. The growth of L5178Y cells was comple tely inhibited by 10(-5) M SL-1250. It should be noted that this growth inhibition was significantly reversed in the presence of equimolar concentrations of guanine, guanosine, or guanosine 5'-monophosphate to those of SL-1250. However, hypoxanthine and xanthine were not effective. These effects of purine addition were observed to be quite similar in growth inhibition by SM-108. It was found that inosine 5'-monophosphate dehydrogenase (EC 1.2.1.14; IMP dehydrogenase), a key enzyme of de novo purine synthesis, from Ehrlich carcinoma cells was inhibited by SM-108 only when 5-phospho-alpha-D-ribose 1-diphosphate (PRPP) and MgCl2 coexisted with SM-108. In contrast, a chemically synthetic ribonucleotide of SM-108 inhibited IMP dehydrogenase without PRPP and MgCl2, and the mode of inhibition was competitive with the Ki value of 2 x 10(-8) M. On the other hand, the inhibition of either growth of L5178Y cells or IMP dehydrogenase in the presence of PRPP and MgCl2 by these compounds was reversed by adenine. A nucleotide of SM-108 was chromatographically identified when [14C]SM-108 was incubated in the enzyme solution with PRPP and MgCl2. This conversion by enzyme was also inhibited by adenine. Viewed together, these results strongly suggest that SL-1250 is, after being converted to SM-108, activated to its nucleotide form by adenine phosphoribosyltransferase (EC 2.4.2.7) and that this SM-108 nucleotide blocks de novo synthesis of guanosine 5'-monophosphate by inhibiting IMP dehydrogenase. (Author abstract) (9 Refs)

26. ADVANTAGES IN THE USE OF L-ASPARAGINASE-ALBUMIN POLYMER AS AN ANTITUMOR AGENT.

Poznansky MJ, Shandling M, Salkie MA, Elliott J, Lau E
Dept. Physiology, Univ. Alberta, Edmonton, Alberta T6G 2H7, Canada
Cancer Res; 42(3):1020-1025 1982

Polymeric conjugates of L-asparaginase and an excess of homologous albumin are compared with free L-asparaginase for antitumor activity using a mouse model 6C3HED lymphosarcoma and a human pancreatic tumor cell line, PANC-1. The asparaginase-albumin polymer is more resistant to proteolytic degradation compared to equivalent amounts of free enzyme and is more effective as an antitumor agent in prolonging survival of C3H/HeJ mice receiving 6C3HED lymphosarcoma. In terms of antitumor activity, the enzyme is approx 20x more effective, compared to free enzyme, when given in polymeric form with albumin. Similarly, the polymeric form of L-asparaginase is more effective in inhibiting cell growth of human pancreatic tumor cells grown in tissue culture. The increased effectiveness of the polymeric form of L-asparaginase is probably related to its resistance to biodegradation. The use of cell surface-specific monoclonal antibodies to target the polymer to tumor cells is also demonstrated. (Author abstract) (31 Refs)

27. CELL POPULATION KINETICS IN RAT PALATAL EPITHELIUM TREATED WITH THE CARCINOGEN 4 - NITROQUINOLINE N-OXIDE (4NQO).

Fisker AV, Karring T
Dept. Oral Pathology, Royal Dental Coll., Vennelyst Blvd., DK-8000 Arhus C, Denmark
J Oral Pathol; 10(6):408-416 1981

Cell population kinetics was investigated in rat palatal epithelium treated with a 0.5% soln of 4-nitroquinoline N-oxide (4NQO) in propylene glycol 3x/wk for 2 wk or 2 mo. Ulcerations were observed in the palatal mucosa 3 days after the first application; all healed after 1 wk. Numerous papillary excrescences were observed on the mucosal surface 1-2 wk after cessation of the 2-wk treatment. The epithelium was hyperplastic; this gradually decreased. No carcinoma or dysplasia was observed. After 2-mo treatment, papillary excrescences were larger than in animals treated for 2 wk. A severely folded hyperplastic epithelium was seen. Carcinomas at the intermolar area developed in three animals. After termination of 4NQO application, the mitotic rates, mitotic counts, and mitotic durations of the experimental animals in both groups were not significantly different from those of the control animals. Thus, under the conditions used, 4NQO did not induce irreversible changes in cell population kinetics of the palatal epithelium. These data indicate that an animal model system resulting in a high incidence of carcinomas should be used when studying cell population kinetics and that stress factors which might induce arrest of mitosis should be avoided. (23 Refs)

28. INHIBITING EFFECT OF DEHYDROASCORBIC ACID ON CELL DIVISION IN ASCITES TUMORS IN MICE.

Poydock ME, Reikert D, Rice J, Aleandri L
Mercyhurst Coll., 501 East 38th St., Erie, PA, 16546
Exp Cell Biol; 50(1):34-38 1982

The transplantable murine ascites tumors, P388 leukemia and Ehrlich carcinoma, demonstrated complete inhibition of mitotic activity after treatment with dehydroascorbic acid in mice. Citric acid at the same pH value (2.4), however, showed no diminution of mitoses. Microscopic examination of the stained ascites exudate taken from the mice treated with 10 mg dehydroascorbic acid revealed few tumor cells and a pronounced increase in white blood cells, whereas the ascites tumor exposed to citric acid appeared normal. (Author abstract) (26 Refs)

29. PROSTATE CARCINOMA TUMOR SIZE IN RATS DECREASES AFTER ADMINISTRATION OF ANTAGONISTS OF LUTEINIZING HORMONE-RELEASING HORMONE.

Redding TW, Coy DH, Schally AV
Endocrine and Polypeptide Lab., Veterans Admin. Medical Center, New Orleans, LA, 70146
Proc Natl Acad Sci USA; 79(4,part1):1273-1276 1982

The effects of two potent antagonistic analogues of luteinizing hormone-releasing hormone (LH-RH) on the growth of two different models of rat prostate tumors have been investigated. Chronic administration of [NAc-p-F-DPhe1,p-Cl-DPhe2,DTrp3,6,D-Ala(10)]LH-RH (antagonist I) at 50 ug/day for 21 days significantly inhibited the growth of the chemical induced squamous cell carcinoma 11095 in Fischer 344 male rats. The weights of the pituitary, ventral prostate, and testes were not significantly altered. After 21 days of treatment with this analogue, serum luteinizing hormone (lutropin), follicle-stimulating hormone, and testosterone levels were markedly decreased. When male Copenhagen F-1 rats bearing the Dunning 3327H prostate adenocarcinoma were injected with antagonist I at 50 ug/day for 6 wk or with [NAc-p-Cl-DPhe1,2,DTrp3,DPhe6,DAla(10)]LH-RH (antagonist II) at 50 ug/day for 17 days, the percentage increase in tumor volume was decreased to half or less and the actual tumor volume was diminished 34-96% compared to controls. Tumor weight was decreased 30% and 89% after antagonist I and II, respectively, compared to untreated controls. The tumor doubling time was 3-to 4-fold longer in rats receiving the inhibitory analogues than in the controls. Treatment with antagonist II decreased the weight of the whole prostate, but neither antagonist

changed the weight of testes, anterior pituitary gland, or adrenals. Serum luteinizing hormone, follicle-stimulating hormone, and testosterone levels in Copenhagen F-1 rats bearing Dunning tumors were significantly decreased after treatment with the inhibitory analogues, but progesterone levels were increased. The inhibitory effects of these antagonistic analogues on rat prostate tumors suggest that these compounds might be considered in the development of new types of therapy for prostate carcinoma and other endocrine-dependent neoplasias. (Author abstract) (32 Refs)

EFFECTS OF PHYSICAL AGENTS ON MITOTIC ACTIVITY

30. X-RAY-INDUCED CELL CYCLE DELAY IN HUMAN LEUKOCYTES: DIFFERENTIAL RESPONSE WITHIN THE FIRST POST-STIMULATION G1-PHASE.

Beek B
Institut fur Genetik, Freie Universitat Berlin, Arnimallee 5-7, D-1000 Berlin 33, W. Germany
Int J Radiat Biol; 41(2):227-230 1982

The effect of x-ray irradiation on cell cycles was studied in human WBC cultures. Cultures were exposed to x-rays at various times after initiation of culture stimulation with phytohemagglutinin. At 74 hr culture time cultures were scored for proportions of first, second, or third divisions. With later irradiation times the proportion of first divisions increased and the proportion of third divisions decreased, indicating that human WBC display increased sensitivity to cycle-delaying effects of x-rays with increasing duration of the first post-stimulation G1-phase. (19 Refs)

31. RADIATION EFFECT ON PARTIALLY SYNCHRONIZED YOSHIDA SARCOMA CELLS.

Bippus PH, Heitz J, Ruhl U, Averdunk R
Inst. Pathology, Free Univ. Berlin, Klinikum Steglitz, D-1000 Berlin, W. Germany
J Cancer Res Clin Oncol; 102(3):253-263 1982

Yoshida sarcoma cells, which have the same growth characteristics as ascites cel ls in the mouse and in cell suspension, were partially synchronized in vitro by means of excess thymidine (0.1 mM thymidine for 18 hr). The growth of non-synchronized cultures was inhibited by irradiation, the degree depending on the dose of radiation. At the same time, a 50% inhibition in vivo (380 rad) and in vitro (480 rad) was determined. The incorporation of 3H-thymidine into the DNA is inhibited by 10-32%, depending on the radiation dose. The mitotic index decreases 2 hr after irradiation by a dose-dependent amount. A mitotic max develops later; the delay is dose-dependent. Partially synchronized cells were irradiated in the G1/S-, S-, G2-, and G1-phase. As compared to the 3H-thymidine incorporation and the mitotic index there were no significant differences between the cultures which were irradiated in the individual phases of the non-synchronized control cultures. The cultures which were irradiated in the G2-phase, however, showed a significantly reduced growth in vivo after 48 hr. If the cells were cultured for more than 72 hr after irradiation, the differences between the cultures irradiated in the G2-phase and the other phases were reduced. (Author abstract) (20 Refs)

32. RADIOSENSITIVITY VARIATION DURING THE CELL CYCLE IN PRONUCLEAR MOUSE EMBRYOS IN VITRO.

Domon M
Dept. Dental Radiology, Tokyo Medical and Dental Univ., 1-5-45 Yushima, Bunkyo-ku, Tokyo, Japan
Cell Tissue Kinet; 15(1):89-98 1982

The radiosensitivity of pronuclear mouse (B6D2 F1 x ICR) embryos has been measured in vitro as a function of time during the cell cycle. This was done by measuring the dose of x-rays (LD50) required to prevent development of 50% of the pronuclear embryos to the blastocyst stage in 5 days of culture. The LD50 was found to vary from 1 to 2 Gy during the period from G1 to the first cleavage. The cell cycle in the pronuclear embryo was analyzed by [3H]thymidine autoradiography. Compared with earlier studies on two-cell mouse embryo radiosensitivity, the pronuclear embryos appear to be more sensitive to radiation than the two-cell embryos. If, however, one considers the radiation sensitivity on a blastomere basis, the pronuclear embryos are not different in their radiation sensitivity from the two-cell embryos. Thus, during the early cleavage stages of mice, radiosensitivity is mainly governed by the content of cells of various cell cycle ages in the embryo. (Author abstract) (33 Refs)

33. EPIDERMAL KINETICS AND ULTRASTRUCTURE OF TOLERANCE TO RADIONECROSIS IN MOUSE TAILS.

Hendry JH, Rushton DA, Allen TD
Paterson Laboratories, Christie Hosp., Manchester, M20 9BX, England
Radiat Res; 89(3):513-527 1982

Epidermal changes in the tails of adult female B6D2F1 mice were studied after administration of 22-44 Gray irradiation. Tails were irradiated at ambient temperature (22-25 C) in air, at 3 7 C in air, or at ambient temperature with 'white spot' nitrogen with a clamp on the tail base to induce hypoxia. Some mice were injected with [3H]thymidine prior to killing in an autoradiographic study to determine the labeling index (LI) and mitotic index (MI). Epidermal changes were examined by light and electron microscopy. Parameters measured included the thicknesses of nucleated and keratinized cell layer, LI and MI in the basal cell layer, detailed surface topography, keratin content, and the time course of recovery of resistance to radiation-induced necrosis. The greatest changes were noted at 3 wk. The epidermis recovered most rapidly between wk 3 and 4, when hyperplasia was constant, but LI and MI were decreasing. Recovery was incomplete at 6 wk. Subnormal keratinization persisted at least until wk 20. When tails were irradiated with 31.5 Gray 6 wk after irradiation with 35 Gray, changes were induced similar to those induced by the first irradiation; these changes appeared approx 1 wk earlier than those appearing after the first irradiation. (30 Refs)

34. UPTAKE OF CYTOSINE ARABINOSIDE (ARA-C) BY LSA LYMPHOMA AFTER IRRADIATION IN THE STATIONARY PHASE OF GROWTH.

Young JA, Maruyama Y
(c/o Maruyama) Dept. Radiation Medicine, Univ. Kentucky Medical Center, Lexington, KY, 40536
Radiology; 142(3):759-763 1982

An in vitro system was used to assess uptake of cytosine arabinoside by LSA ascites tumor cells growing in vivo. Changes in tumor uptake with aging after depopulation and perturbation of the cell population with 1,000 rad were studied. Both DNA synthesis and drug uptake were highest during early rapid

tumor growth and decreased with aging and the stationary phase of growth. However, irradiation caused a second peak of cellular activity and drug uptake. These results indicate that irradiation stimulates regrowth of tumor. (Author abstract) (33 Refs)

35. MODIFICATION OF RADIATION-INDUCED DIVISION DELAY BY CAFFEINE ANALOGUES AND DIBUTYRYL CYCLIC AMP.

Kimler BF, Snyder MH, Rowley R, Schneiderman MH
Lab. Experimental Radiation Oncology, Thomas Jefferson Univ. Hosp., Philadelphia, PA, 19107
Int J Radiat Biol; 41(1):47-58 1982

The mitotic selection procedure for cell cycle analysis was utilized to investigate the concentration-dependent modification of radiation-induced division delay in Chinese hamster ovary (CHO) cells by methyl xanthines (caffeine, theophylline, and theobromine) and by dibutyryl cyclic AMP. The methyl xanthines (concentrations from 0.5 to 1,000 ug/ml) all reduced radiation-induced division delay with the effect being linear between approximately 100 and 1,000 ug/ml. After doses of 100-300 rad, delay was reduced by 75, 94 or 83% at 1,000 ug/ml for each drug, respectively. However, the addition of dibutyryl cyclic AMP had an opposite effect: radiation-induced delay was increased by the concentrati on range of 0.3 to 300 ug/ml. These results indicate that in mammalian cells the control of cell cycle progression and the modification of radiation-induced division delay are not simply related to intracellular levels of cyclic AMP. Rather, there appear to be at least two competing mechanisms which are differentially affected by caffeine analogues or by direct addition of dibutyryl cyclic AMP. The direct effect of caffeine and the methyl xanthines on membrane calcium permeability is considered. (Author abstract) (31 Refs)

36. THE MAMMALIAN RADIATION SURVIVAL CURVE.

Bloomer WD, Adelstein SJ
Harvard Medical Sch., 50 Binney St., Boston, MA, 02115
J Nucl Med; 23(3):259-265 1982

Cell death from ionizing radiation is the result of chemical alterations in the genome. For cells grown in culture, various mathematical equations have been proposed to describe the loss of reproductive capacity. Based on target theory, they provide a convenient description of radiation dose-response curves and allow the calculation of characteristic parameters for comparative radiation studies. Recovery processes, including redistribution, repair, repopulation, recruitment, and reoxygenation (in tumors only) play an important role in the final expression of cellular damage. (Author abstract) (25 Refs)

37. RECOMBINATION AND MUTAGENESIS IN RAD6 MUTANTS OF SACCHAROMYCES CEREVISIAE: EVIDENCE FOR MULTIPLE FUNCTIONS OF THE RAD6 GENE.

Montelone BA, Prakash S, Prakash L
(c/o L. Prakash) Dept. Radiation Biology and Biophysics, Sch. Medicine, Univ. Rochester, Rochester, NY, 14642
MGG; 184(3):410-415 1981

The rad6-1 and rad6-3 mutants are highly UV sensitive and show an increase in spontaneous and UV induced mitotic heteroallelic recombination in diploids. Both rad6 mutants are proficient in spontaneous and UV induced unequal sister chromatid recombination in the reiterated ribosomal DNA sequence and are deficient in UV induced mutagenesis. In contrast to the above effects where both mutants appear similar, rad6-1 mutants are deficient in sporulation and meiotic recombination whereas rad6-3 mutants are proficient. The differential effects of these mutations indicate that the RAD6 gene is multifunctional. The possible role of the RAD6 gene in error prone excision repair of UV damage during the G1 phase of the cell cycle in addition to its role in postreplication repair is discussed. (Author abstract) (41 Refs)

38. RECOVERY AFTER EXPOSURE TO NEAR-ULTRAVIOLET LIGHT OF CELLS CONTAINING 5-BROMODEOXYURIDINE.

Hagan MP, Elkind MM
(c/o Elkind) Mammalian Cell Biology Group, Div. Biological Medical Res., Argonne Natl. Lab., Argonne, IL, 60439
Biophys J; 34(3):367-374 1981

Effects of near-UV irradiation were examined in synchronized Chinese hamster cells pulse-labeled with bromodeoxyuridine at times in the cell cycle when a shoulder-type survival curve appeared. Such cells were able to repair sublethal damage and potentially lethal damage expressed by caffeine. Kinetics of the two processes differed. In template-labeled cells, time is apparently inadequate to effect prereplication repair; effective contributions to cell survival from other types of DNA repair processes are precluded. (19 Refs)

39. EFFECTS OF HYPERTHERMIA ON DIVIDING CHINESE HAMSTER OVARY CELLS AND ON MICROTUBULES IN VITRO.

Coss RA, Dewey WC, Bamburg JR
Dept. Radiation Therapy and Nuclear Medicine, Thomas Jefferson Univ. Hosp., Philadelphia, PA, 19107
Cancer Res; 42(3):1059-1071 1982

The ultrastructure of Chinese hamster ovary cells was examined immediately after heating cells in mitosis, and the findings were compared with (a) the behavior of heated cells monitored with time lapse cinematography following heat shocks and (b) proliferative survival of individual cells followed for 7 days after heating. Treatment of dividing cells at 45.5 C (5 to 15 min) disassembled the spindle and disrupted both the contractile ring and the midbody-cytoplasmic bridge complex to varying degrees depending on the length of heating. The spindle did not reform upon return to 37.0 C. Microtubular proteins were heated in vitro to determine if their inactivation was responsible for the inability of the spindle to reform. Heat completely disassembled the intact microtubules and inactivated a proportion of the microtubular proteins in vitro; however, a fraction of the microtubular proteins from heat-disassembled microtubules still was capable of reassembly. The time lapse studies indicated that cells in division at the time of heating entered G1 without completing division. Of the resultant tetraploid cells, 88% had greater than or equal to 2 nuclei; 59% of the tetraploid cells divided 35 -7 (S D) hr following the heat shock (control generation time, 13 -2 hr), and 95% of the flattened progeny had more than one nucleus. The fate of individual cells that were in mitosis or G1 when treated at 45.5 C for 4.5 min was monitored for 7 days. The survival of the total heated population of cells was 19%, but the surviving cells were almost totally accounted for by the G1 cells present as contaminants in the heated population. Less than 2% (2 of 115) of the monitored cells that were heated in mitosis formed colonies. Therefore, the morphological disruption of the spindle, contractile ring, or midbody-cytoplasmic bridge complex by a heat of 45.5 C prevented cytokinesis, and the resultant tetra-

ploid cells became proliferatively dead. (Author abstract) (34 Refs)

OTHER RELATED STUDIES

40. EFFECTS OF DELAYS IN THE CELL CYCLE ON THE INDUCTION OF PRENEOPLASTIC AND NEOPLASTIC LESIONS IN RAT LIVER BY 1,2-DIMETHYLHYDRAZINE.

Ying TS, Enomoto K, Sarma DS, Farber E
Dept. Pathology, Univ. Toronto, Toronto, Ontario M5G 1L5, Canada
Cancer Res; 42(3):876-880 1982

This study was designed to explore further the relationship between cell proliferation and the induction of early putative preneoplastic lesions by carcinogens. Rats were given a non-necrogenic dose of 1,2-dimethylhydrazine 24 hr before being subjected to partial hepatectomy. Beginning 4 hr later, hydrocortisone was injected 10x at 4-hr intervals to delay progression through the cell cycle, including inhibition of DNA synthesis by at least 85% for about 40 hr. At the appropriate time thereafter, the putative preneoplastic hepatocytes were selectively stimulated to grow in vivo into gamma-glutamyltransferase-positive focal lesions. Animals given hydrocortisone showed a large decrease (71%) in the number of gamma-glutamyltransferase-positive foci. In contrast, when hydrocortisone was given at 6 days after partial hepatectomy, no inhibition in the induction of hepatic lesions was observed. In the next experiments, rats were treated with 1,2-dimethylhydrazine and were subjected to partial hepatectomy at 12, 24, or 84 hr or 1 wk thereafter. A significant number of gamma-glutamyltransferase-positive foci was found when partial hepatectomy was performed at 12 or 24 hr but far fewer were found when the operative partial hepatectomy was delayed to 48 hr or 1 wk later. Similarly, in long-term experiments, 6 of 14 animals developed primary hepatocellular carcinoma 13 mo after the time of injection of 1,2-dimethylhydrazine when partial hepatectomy was performed at 12 hr, while none of the animals developed liver cancer when the operation was performed at 48 hr. These results imply that the majority of biochemical lesions induced by 1,2-dimethylhydrazine that are relevant to the induction of liver preneoplasia and neoplasia are short-lived and that their persistence is associated with some cellular activity closely related to the cell cycle. (Author abstract) (39 Refs)

41. RETINOL (VITAMIN A) INHIBITS SISTER CHROMATID EXCHANGES AND CELL CYCLE DELAY INDUCED BY CYCLOPHOSPHAMIDE AND AFLATOXIN B1 IN CHINESE HAMSTER V79 CELLS.

Huang CC, Hsueh JL, Chen HH, Batt TR
Dept. Experimental Biology, Roswell Park Memorial Inst., 666 Elm St., Buffalo, NY, 14263
Carcinogenesis; 3(1):1-5 1982

Retinol (vitamin A alcohol) at the doses tested neither induced an increase of frequency of sister chromatid exchanges (SCE) nor cell cycle delay in Chinese hamster V79 cells with or without the metabolic activation of S-9 mix. However, it inhibited SCE frequencies and cell cycle delay in V79 cells induced by the indirect mutagen cyclophosphamide or aflatoxin B1. The inhibition was found to be dose and time dependent. These results suggest that retinol itself may have no direct effect on the genetic mat erials but rather exert its effects possibly by inhibiting the metabolic activation of an indirect mutagen or carcinogen. Thus, the antitumor activities of retinoids may not be limited to the widely accepted role of the preventing the promotion step but also the initiation step of carcinogenesis. (Author abstract) (33 Refs)

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